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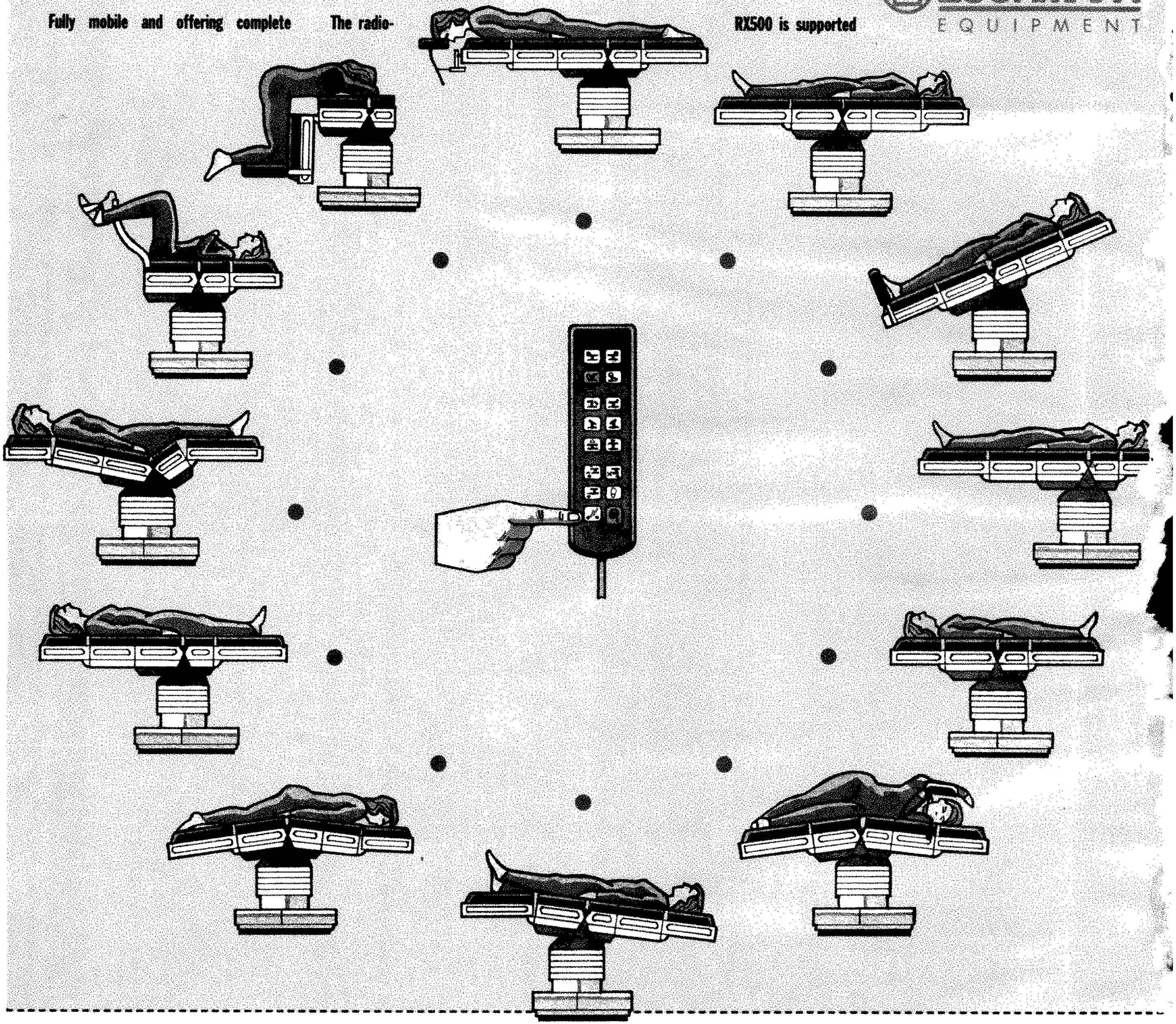

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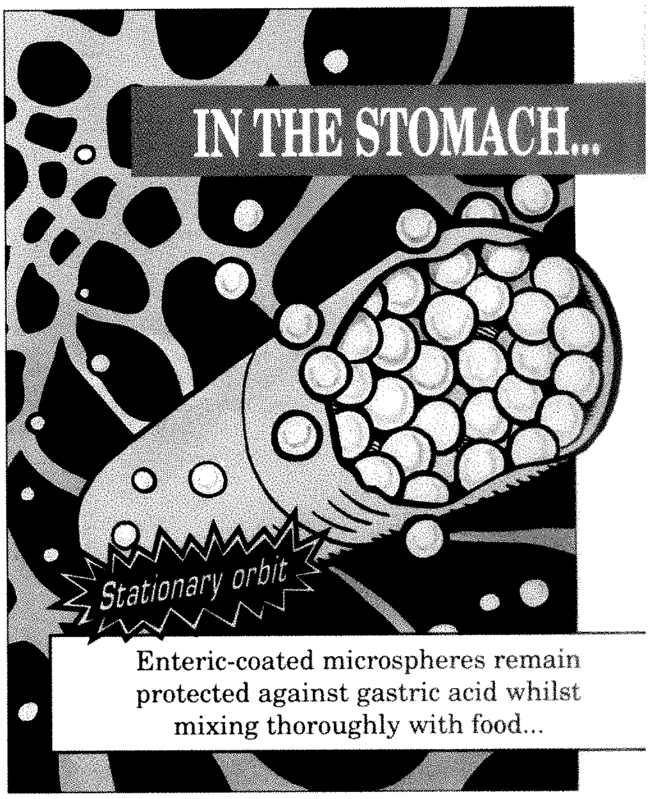

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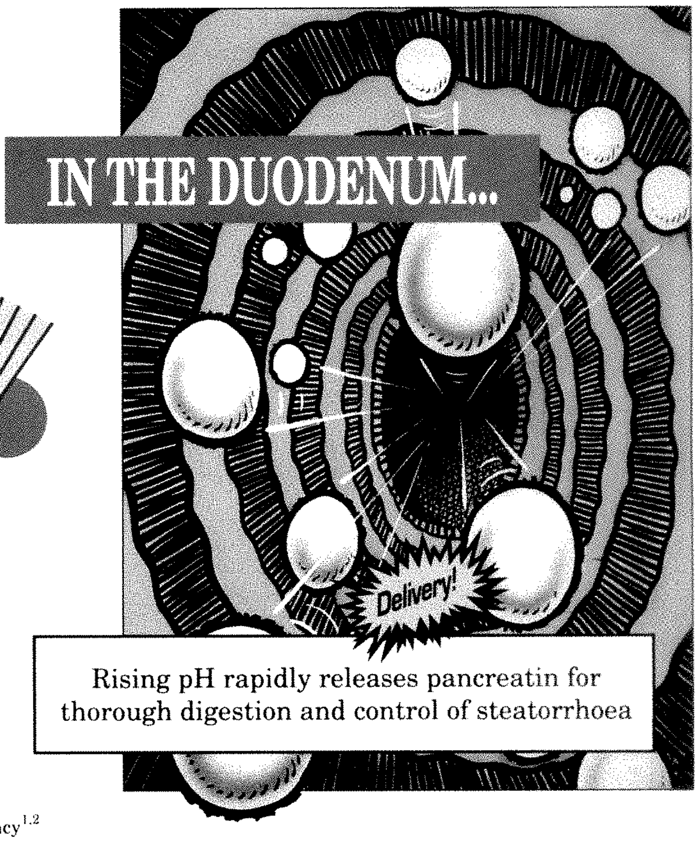
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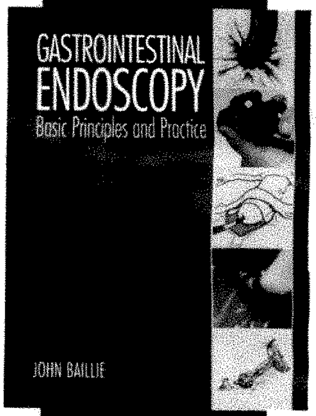

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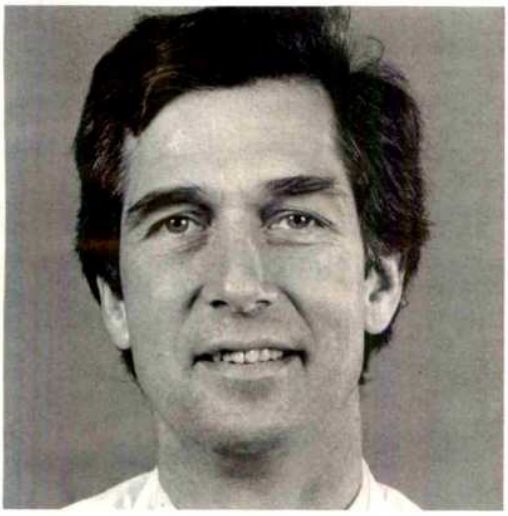
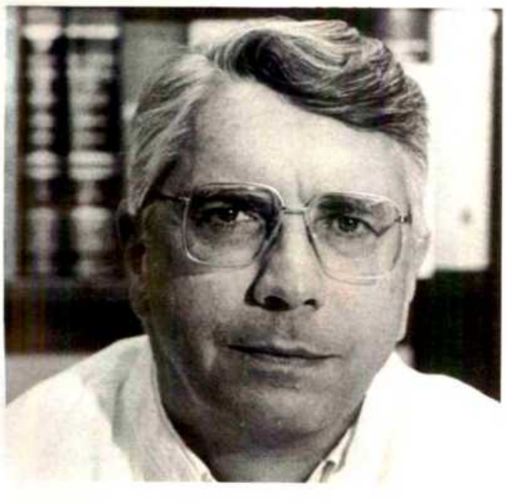
The overseas membership of the Editorial Board has increased steadily over the past two decades, reflecting the international flavour of The British Journal of Surgery. *In 1989, to foster closer links with continental Europe, the Council of the BJS Society appointed the first surgeon from outside Britain to join the Editorial Committee, the body with executive control over the monthly publication of the Journal. There are now three representatives from mainland Europe on the Editorial Committee, and their profiles are given below.*



PROFESSOR CRISTOBAL PERA

(Spain)

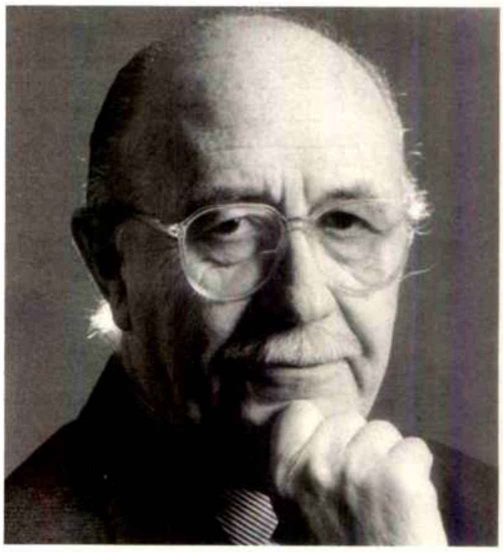
Cristobal Pera (*right*) is Professor of Surgery in the University of Barcelona. Born in 1927, he trained in Seville and Valladolid before taking up his present post in 1966. He became an Honorary Fellow of The Royal College of Surgeons of England in 1988 and served as President of the Catalan Surgical Society from 1986 to 1990. In 1974 he founded the Journal *Revista Quirúrgica Española*. He joined our Editorial Board in 1986 and was soon active in establishing the Spanish edition of *The British Journal of Surgery*, which now appears on a regular basis 3 months after the corresponding English version. The circulation has grown to embrace nearly 2000 subscribers throughout Spain and Latin America. The success of the Spanish edition is very largely due to Professor Pera, who selects the papers and supervises their translation.



PROFESSOR HANS JEEKEL

(The Netherlands)

Johannes Jeekel (*left*) was born in 1941 and graduated from Leiden University in the Netherlands. He spent 2 years as a Clinical and Research Fellow in Surgery at the Massachusetts General Hospital, Boston, USA, before continuing his residency training at Dijkzigt University Hospital in Rotterdam. He completed a thesis *cum laude* on the immunological enhancement of skin grafts in 1972. He was appointed successively surgeon to the Medical Faculty at Dijkzigt (1974), staff surgeon at Maastricht (1976), and Professor of Surgery at Erasmus University and Dijkzigt Hospital, Rotterdam (1980). Since 1987 he has been Head of the Department of Surgery at Dijkzigt. Professor Jeekel joined the Editorial Board of the Journal in 1987 and the Editorial Committee in 1989.



PROFESSOR CHRISTIAN HERFARTH

(Germany)

Christian Herfarth (*left*) has been Editor-in-Chief of our sister journal *Der Chirurg* for the past 10 years. He was born in 1933 and graduated from Heidelberg University in 1957 *summa cum laude*. He became an Associate Professor at Marburg in 1966 before moving to Freiburg, where he was promoted to be Professor of Surgery in 1972. The following year he moved to Ulm as Head of the Department of General Surgery and then in 1981 to Heidelberg, where he is now Head of the Department of Surgery. From 1989 to 1991 he served as Dean of the Faculty of Medicine and in 1987 was President of the German Society of Gastroenterology. In 1991 Professors Herfarth and Pera joined Professor Jeekel on the Editorial Committee of *The British Journal of Surgery*.

Robin Williamson

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Laparoscopic operations in paediatric surgery

There appears little doubt that it will be possible in time to perform most, if not all, surgical procedures by minimally invasive techniques. Once the present process of training and 'retooling' of general surgeons is complete, it is likely that any operation that can be performed by open methods will be able to be performed endoscopically. The 'second wave' of endoscopic instruments now becoming available in this country, such as needle-holders, tissue forceps and so forth, has shown that all instrument types currently employed in open surgery can be modified for endoscopic use. Techniques developed for laparoscopic operations within the gas-filled peritoneal cavity have already been extended for use within the tissue planes of cleavage, such as subfascial ligation of incompetent perforating veins, inguinal herniorrhaphy, and oesophagectomy. The term 'endoscopic' surgery may become more useful than 'laparoscopic' surgery.

In general surgery, those who have conquered the summit of laparoscopic cholecystectomy have had revealed to them a whole range of similar pinnacles, such as colectomy, bile duct exploration and vagotomy; some are more distant than others. There is little doubt, however, that none of these would have been contemplated or have become feasible without the initial breakthrough of laparoscopic cholecystectomy.

While the electricity of laparoscopic surgery has already touched most general surgeons, this technical revolution has only recently begun to spread into paediatric surgery. Paediatric laparoscopy lagged behind the advances in adult endoscopy partly because the reduction in size of the instruments meant small views and poor images. However, in 1971 Gans and Berci[1] described how technical advances had improved laparoscopic methods in paediatrics and advocated their use in the differential diagnosis of biliary atresia and choledochal cysts, liver biopsy, and the assessment of intersex by the inspection of pelvic organs. Berci *et al.*[2] reported 500 diagnostic laparoscopies, mainly in adults but including children as young as 18 months. Further extension of diagnostic laparoscopy has occurred in the evaluation of the impalpable or intra-abdominal testis[3,4], and in the assessment of the acute abdomen and possible appendicitis in childhood[5].

More recently there has been increasing interest in performing conventional procedures in paediatric surgery by laparoscopic surgical techniques, the main areas being the intra-abdominal testis, appendicectomy, cholecystectomy and pyloromyotomy. The Fowler–Stephen technique of staged mobilization of the intra-abdominal testis has been adapted so that the first stage is carried out laparoscopically. Preliminary clipping of the spermatic vessels leads to augmentation of the collateral vasal blood supply, and a vas-based orchidopexy 6 months or more later can be successfully performed through an inguinal incision[6]. Laparoscopic appendicectomy was described by Semm[7] and several series have reported the advantage of this technique even in the acutely inflamed and perforated appendix. Gotz *et al.*[8] reported the results of 388 laparoscopic appendicectomies (40 per cent paediatric). There were no deaths. Only 3 per cent of operations (occurring in the first 50 cases) had to be converted to open procedures and two of these were complicated by abscess formation. Cholelithiasis is not a common condition in childhood but it does occur in certain circumstances, such as sickle cell disease and other haemoglobinopathies, and if symptomatic requires cholecystectomy. Laparoscopic cholecystectomy in the paediatric patient has been described, based largely on adult experiences but modified to suit the different abdominal cavity[9]. The outcome is analogous to that in adult surgery – reduced hospital stay (mean 28·5 h) and earlier return to school (within a week)[10]. It has also been possible to modify the traditional Ramstedt pyloromyotomy by laparoscopic incision and spread of the pyloric tumour[11].

Before laparoscopic procedures become widely adopted in paediatric surgery, careful attention will have to be paid to the appropriate training of surgeons; an awareness of the differences between the paediatric and adult patient is essential. For instance, the presence of an unrecognized patent processus vaginalis or hernial sac,

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not an uncommon feature in the infant, can lead to a painful scrotal emphysema after operation. Consideration must be given to the size, placement and position of the cannulas, and to the efficacy and safety of pressures for both suction and insufflation. However, early experience is showing that laparoscopic surgery in paediatric patients is feasible and that it can be performed safely.

I predict that many, if not most, neonatal and paediatric surgical procedures will eventually be performed endoscopically. Experience with the high-speed electrical tissue morcellator[12] will allow removal of solid organs, such as kidney and spleen, which are broken up and then aspirated. Benefits to the child would be reduced hospital stay, in some cases outpatient rather than inpatient treatment, less pain and resultant distress to child and parents, fewer complications, and improved cosmetic appearances. Furthermore, it is not fanciful to predict similar operative treatment on the fetus at an optimum time within the amniotic fluid.

One can be certain that these developments would have had the blessing of Dennis Brown, the great innovator, inventor and champion of surgery in children. In establishing surgical principles in paediatric surgery he emphasized the importance of adequate illumination of the operative field, instrument design, and minimal tissue handling, but 'most important of all a surgeon especially skilled and interested in such cases'.

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Tests of anorectal function

The management of defaecatory disorders is often challenging, especially when the underlying abnormality is a disturbance of anorectal function. The symptoms produced by such disorders are usually unpleasant and at times cause great distress. The outcome of remedial surgery is often unpredictable and may be disappointing, so it is not surprising that the surgeon looks to specialist investigations for help in selecting the most appropriate treatment. In this context, an ideal test of anorectal function is one that can define underlying abnormalities with a high degree of sensitivity and specificity, predict their natural history, and indicate the likely outcome of surgery.

In some circumstances these criteria can all be satisfied. A good example is the use of anorectal manometry in the investigation of adult constipation, where the absence of a rectoanal inhibitory reflex indicates myenteric aganglionosis and thus Hirschsprung's disease[1]. Manometry will not only diagnose or exclude the disorder, but the anal pressure profile will also provide useful information on the selection of patients for surgery. Unfortunately, only a tiny minority of adult patients with constipation have Hirschsprung's disease and many surgeons insist on taking a full-thickness rectal biopsy for histological examination to corroborate manometric findings. In practice, this approach diminishes the value of the investigation to that of a screening exercise.

Other instances in which tests of anorectal function can make an important contribution to management are the use of concentric-needle electromyography in the diagnosis and localization of sphincter tears, and the use of nerve conduction studies in the assessment of incontinence (if this defines a treatable lesion such as cauda equina compression caused by intervertebral disc prolapse). In both instances, however, anorectal function tests may soon be superseded by new radiological techniques such as anal endosonography and magnetic resonance imaging.

Most other disorders of anorectal function are less easy to define. The causes of idiopathic anorectal incontinence and obstructed defaecation are unknown and, at the time they present (perhaps many years after an initial insult), they are associated with physiological abnormalities that are complex, diffuse and poorly understood. Furthermore, current treatments have only limited success and the relationship between the abnormalities detected and the outcome of treatment is rarely obvious.

In idiopathic anorectal incontinence the sphincter is short and weak, rectal compliance is reduced, sampling is abnormal and anorectal sensation is diminished[2,3]. A ubiquitous feature is an electromyographic change consistent with denervation and subsequent reinnervation of the striated muscle of the external sphincter and pelvic floor. This observation is not diagnostic, however, since equivalent changes may be found in the same muscles of subjects who are normally continent[3]. The extent of the manometric and electromyographic abnormality demonstrated cannot be used reliably to forecast the outcome of surgery, even though predictive differences have been reported between some groups of patients[4]. Verification of these findings is required.

The investigation of obstructed defaecation has also proved disappointing. Two phenomena are commonly demonstrated, both of which are thought to be responsible for the presenting symptoms. First, inappropriate contraction of the puborectalis occurs during defaecation (anismus), which is demonstrated by a recording of increased electromyographic activity in the puborectalis during attempted defaecation. Second, internal rectal intussusception occurs; this can be detected at sigmoidoscopy but is more commonly diagnosed by evacuation proctography. Whether or not these findings truly reflect abnormal anorectal behaviour is questionable, as both may be demonstrated in normal asymptomatic individuals[5,6] and symptoms may persist in spite of apparently effective treatment[7,8].

In addition to its role in the assessment of anorectal dysfunction, manometry is used widely in the assessment of patients about to undergo sphincter-preserving surgery for inflammatory bowel disease or carcinoma. However, the experienced surgeon can obtain just as much information from digital examination[9], and in reality few patients are refused surgery solely on the basis of an abnormal anal canal pressure profile. A pressure gradient between the rectum and anus is essential but it is not the only factor preserving continence. This issue highlights an important deficiency for, until recently, tests of anorectal function have focused on the measurement of

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phenomena in isolation, often for relatively short periods of time and in the artificial environment of the anorectal physiology laboratory. To overcome this deficiency, ambulatory as well as integrated monitoring techniques have been introduced. Several measurements can now be made simultaneously and recorded for a number of hours as the patient undertakes normal activities. These provide a more natural and global picture of anorectal activity but are time consuming to obtain and, with increasing complexity, more difficult to interpret. They are also unlikely by themselves to reveal much about the mechanisms, neural and muscular, that subserve normal anorectal function. Insight into these more fundamental aspects of anorectal physiology will be gained only through basic scientific research.

In summary, tests of anorectal function have made a major contribution to the understanding of normal and abnormal anal sphincter activity, but they have not so far lived up to expectation in clinical practice. While every self-respecting colorectal surgery department should have a physiology laboratory and patients should be studied, there is still no substitute for clinical acumen and a healthy realism in the selection of patients for surgery.

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Cytokines in tumour therapy

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Cytokines are low molecular weight proteins released by cells of the immune system that have therapeutic potential in cancer. They include the interleukins, the interferons, tumour necrosis factor and the colony-stimulating factors. Cytokines are capable of producing significant and sustained responses against a number of tumours. Clinically, the highest response rates to cytokine immunotherapy have been seen in melanoma and renal cell cancer. Current efforts aim to reduce treatment-related toxicity while maintaining the efficacy of cytokines. The therapeutic potential of these agents may be increased with genetic manipulation by introducing genes encoding cytokines into tumour-infiltrating lymphocytes and certain tumour cells. However, immunotherapy remains time consuming and expensive, and further developments are necessary before it can have a definitive role in tumour management.

Despite advances in surgical technique and improvements in chemotherapy, the ability to cure many patients with cancer still remains an ideal rather than a reality. There is a consensus that the three classic approaches to cancer treatment, i.e. surgery, radiotherapy and chemotherapy, have reached a plateau[1], although further developments in these will probably lead to refinements in the management of malignant disease. It has long been recognized that the immune system plays a pivotal role in the patient's response to disease. Recently, cancer therapies have therefore been directed at modulation of components of the immune system. In particular, 'immune messengers' or cytokines may play a vital role in regulating host antitumour defence mechanisms. Knowledge of cytokines and their functions is expanding rapidly[2]; this article reviews the cytokines and discusses their potential role in the treatment of malignant disease.

Cytokines are low molecular weight (10–50 kDa) proteins released by cells of the immune system. They bind with extreme specificity and great affinity to receptors on target cells and regulate their proliferation, differentiation and functional activation[3]. Cytokines produced by lymphocytes are called lymphokines; those produced by mononuclear phagocytes are called monokines. Cytokines are different from endocrine hormones in that they are produced by a number of cells rather than by specialized glands. They are not usually present in detectable levels in the serum and generally act on target cells in a paracrine (i.e. locally near the producing cells) or autocrine (i.e. directly on the producing cells) manner. Different cytokines display considerable overlap in their biological activities. The elucidation of various *in vitro* and *in vivo* properties of these proteins has led to their introduction into clinical medicine as therapeutic agents in the treatment of infection and cancer. The cytokines that have been shown to have therapeutic potential in treating cancer include the interleukins, the interferons, tumour necrosis factor (TNF) and the colony-stimulating factors.

Interleukins

The interleukins are a family of protein molecules that are fundamental to both cellular and humoral immune responses. At least 11 different types have been described, many with a potential antineoplastic role.

Interleukin 1

Interleukin 1 (IL-1) was originally described in the 1940s as 'endogenous pyrogen' because of its ability to produce fever when injected into experimental animals[4]. Two polypeptide forms are now recognized: IL-1α and IL-1β. IL-1α is cell associated and thought to be involved in antigen presentation[5]. IL-1β is the predominant form and is readily secreted from macrophages. Although they have only limited amino acid sequence identity, IL-1α and IL-1β recognize the same receptor and share the same biological properties. IL-1 is synthesized predominantly by mononuclear phagocytes, but can also be derived from a variety of other cells including endothelial cells, keratinocytes, neutrophils and B lymphocytes[6].

The actions of IL-1 have been elucidated in recent years. T cells proliferate at accelerated rates in the presence of IL-1 in response to mitogen[7] IL-1 stimulates T cell proliferation by inducing production of interleukin 2 (IL-2) as well as increasing the number of IL-2 receptors on the T cell. It acts as an endogenous pyrogen[8] by stimulating local release of prostaglandins in the anterior hypothalamus and induces anorexia by acting on the central satiety centre. Furthermore, IL-1 attenuates the perception of pain after injury or inflammation by increasing the release of β-endorphins and increasing the number of opiate-like receptors in the brain[8]. It also protects against the effects of lethal radiation[9]. The metabolic effects of IL-1 include induction of hepatic acute-phase proteins, remodelling of connective tissue and bone during injury and inflammation, stimulating the activity of osteoclasts in bone, and degradation of collagen and proteoglycan in connective tissue[4].

Recombinant IL-1 is cytostatic towards human melanoma tumour cells *in vitro*[10]. Human peripheral blood monocytes stimulated with lipopolysaccharide release a substance with an activity that is cytotoxic for the A375 melanoma cell line. Biochemical and immunological characterization of this substance indicate that it is IL-1β. Finally, human recombinant IL-1β, purified to homogeneity, is directly cytotoxic for the A375 cell line[10].

IL-1 is identical to 'endogenous pyrogen' and its administration induces severe pyrexia, an unacceptable side-effect[11]. Although Lachman *et al.* have demonstrated that it has antitumour properties[10], IL-1 has not been employed in clinical trials because of these side-effects.

Interleukin 2

IL-2 was first characterized in 1976 by Morgan *et al.*, who reported the discovery of a protein, produced by normal peripheral blood lymphocytes, that induced proliferation of stimulated T lymphocytes[12]. This 15·5-kDa glycoprotein was

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initially called T cell growth factor but subsequently renamed IL-2. It is the pivotal molecule in the maintenance of an intact immune system and stimulates both T and B cell immunity. IL-2 is a vital cofactor in the development of cytotoxic T lymphocyte activity against tumours. In addition to its T cell growth-promoting effects, which allow maintenance of T cell lines and clones, IL-2 participates in tumoricidal activity[13,14] through growth of natural killer (NK) and lymphokine-activated killer (LAK) cells[15]. IL-2 also augments B cell growth and immunoglobulin production[16], and enhances interferon gamma (IFN-γ) production[17]

A number of studies using recombinant interleukin 2 (rIL-2) in both experimental animals and humans have shown that it has some activity against a variety of cancers[18,19]. Clinical immunotherapy protocols with IL-2 were initiated in 1980 in the Surgery Branch of the US National Cancer Institute when cultured peripheral blood lymphocytes were safely infused into three patients[20] Early efforts at adoptive immunotherapy[21] dealt with NK cells activated either by the lectin phytohaemagglutinin or by crude culture supernatants containing IL-2. Subsequent studies used purified homogenous natural IL-2 derived from the Jurkat high-producer cell line[22]. When bacterially produced rIL-2 became available this was used in clinical trials. More recent studies[23–25] have utilized either high doses of rIL-2 alone or the adoptive transfer of LAK cells generated using rIL-2. In 1985 the first report was published documenting tumour regression in patients with melanoma following administration of IL-2 with LAK cells[24] LAK cells are peripheral blood lymphocytes that can be generated *in vitro* by incubation with high-dose IL-2. They possess the ability to kill cancer cells but not normal cells. IL-2 is used in combination with LAK cells to produce a more potent antitumour response[25,26].

Cytotoxic T lymphocytes are a subset of T cells that kill target cells expressing specific antigen. To recognize and respond to a foreign antigen, a T cell must be presented in a complex with a self major histocompatibility complex (MHC) molecule. The expression of MHC proteins on tumour cells may be critical for their immunological recognition and destruction. NK cells are effector cells of natural and acquired immune responses to tumours. They utilize the same lytic mechanisms as cytotoxic T lymphocytes to kill tumour cells; however, they do not express T cell antigen receptors and they kill targets in an MHC-unrestricted manner. This difference in mechanism of action may explain why melanoma responds to cytotoxic T lymphocyte-specific therapy whereas other tumour types tend not to respond.

Tumour-infiltrating lymphocytes are lymphoid cells that infiltrate solid tumours and can be grown[20] by culturing suspensions of lymphoid cells from tumours in IL-2 Tumour-infiltrating lymphocytes obtained from some human melanomas have unique lytic specificity for autologous tumours[27,28] and the use of tumour-infiltrating lymphocytes and IL-2 together can mediate substantial tumour regression in some patients with advanced malignant melanoma[29,30]. Kradin *et al.*[31] reported objective tumour responses lasting 3–14 months in 29 per cent of patients with renal cell cancer and 23 per cent of those with melanoma treated with tumour-infiltrating lymphocytes and IL-2.

Further potential for IL-2 in antitumour therapy has been established by using rIL-2 in combination with other cytokines[32]. In several murine tumour models, rIL-2 in combination with recombinant interferon alpha (IFN-α) elicits a potent antitumour response which is often greater than that which can be reached with the individual agents at non-toxic doses[33]. IL-2 *in vitro* promotes the release of cytokines, including IFN-γ and TNF, which also possess antileukaemic activity and can enhance granulocyte function. This secondary cytokine release of IFN-γ and TNF by IL-2 may contribute to the antileukaemic effects of IL-2 in patients following bone marrow transplantation or chemotherapy[34]. Bello-Fernandez *et al.* have shown that interleukin 4 (IL-4) acts as a homoeostatic regulator of IL-2-induced TNF and IFN-γ release[35]. The addition of recombinant IL-4 to IL-2-stimulated cultures leads to significant inhibition of IFN-γ and TNF production Since both TNF and IFN-γ may contribute to the antineoplastic action of IL-2, manipulating the level of IL-4 activity *in vivo* could augment the benefits of IL-2 immunotherapy[35]. IL-2 in combination with interferon beta (IFN-β) has been shown to have a 27 per cent objective response rate in 22 patients with advanced renal cell carcinoma[36].

IL-2 has been given to patients in combination with chemotherapeutic agents in an attempt to obtain possible synergistic effects. A regimen using low-dose cyclophosphamide (350 mg m^{-2}) in combination with IL-2 in 32 patients with either malignant melanoma or renal cell carcinoma achieved only minor antitumour activity[37]. Dillman *et al.* evaluated rIL-2 plus LAK cells alternating with sequential dacarbazine chemotherapy in 27 patients with metastatic melanoma[38]. This therapeutic protocol was reasonably tolerated, but the response rate was not significantly better than that achieved with other IL-2 regimens or with chemotherapy alone[38]. Paciucci *et al.* administered IL-2 with weekly doxorubicin to 12 patients with advanced malignancy[39], demonstrating a partial response in five. However, toxicity of the regimen proved to be a significant problem.

The most significant antitumour responses associated with IL-2 therapy have been identified in the treatment of malignant melanoma[40–42] and renal cell carcinoma[43–51]. Other tumours treated with IL-2 include gliomas[52,53], bladder[54,55], ovarian[56], neuroblastoma[57], lung[58], head and neck[59], breast, lymphoma, colon and mesothelioma[19].

IL-2 therapy is associated with significant side-effects including pronounced fluid retention, anaemia, thrombocytopenia and hypotension[60]. Marked immunological changes have been observed in patients receiving this cytokine: raised levels of lymphocytes bearing IL-2 receptors, free circulating IL-2 receptors, and the presence of monocytes bearing IL-2 receptors[61]. The significance of these findings is unknown, but they occur in the presence of a marked lymphopenia which resolves within 48–72 h. Regrettably, there seems little doubt that intravenous IL-2 therapy alone is toxic. A review of 285 patients with renal cell carcinoma treated with IL-2 alone demonstrated that the antitumour activity was dependent on both schedule and intensity of the dose administered[62]. Controversy persists over the relative merits of regimens devised to reduce the toxicity; Rosenberg has described a high-dose bolus regimen[18] while West *et al.* have utilized a continuous-infusion regimen[19].

IL-2 is the first cytokine to be employed widely in clinical trials. It provides significant antitumour responses in patients with malignant melanoma and renal cell carcinoma, but its side-effects have limited greater clinical use. Usage will expand with the further development of adoptive immunotherapy using LAK and tumour-infiltrating lymphocytes as well as in combination with other cytokines.

Interleukin 3

Interleukin 3 (IL-3) is released from T cells stimulated with the mitogen phytohaemagglutinin[63]. Synonyms for this cytokine are 'colony forming unit-stimulating activity' and 'multi-colony stimulating factor'. Murine IL-3 is a polypeptide of 133 amino acids with a molecular weight[64] of 30–40 kDa. IL-3 is produced by T lymphocytes as well as by a monomyelocytic cell line (WEHI 3), and activates lymphocytes as well as mast cells[65]. Reported activities include the stimulation of mast cells, neutrophils, macrophages and megakaryocytes from isolated haematopoietic progenitors[66]. To date, no study has identified IL-3-mediated antineoplastic activity, but this cytokine has a role in increasing platelet and neutrophil counts in patients with advanced malignancy[67].

Phase I and II trials with recombinant human interleukin 3 (rIL-3) expressed in yeast have been carried out in patients with advanced malignancy as well as in those with bone marrow suppression. Subcutaneous administration of rIL-3 at doses of 30–500 μg m^{-2} for 15 consecutive days in patients with advanced malignancy but normal haematopoiesis resulted in a dose-dependent increase in platelet counts, as well as a substantial increase in the number of circulating neutrophils, eosinophils, monocytes, and lymphocytes[67]. In patients with secondary haematopoietic failure caused by prolonged chemotherapy[68], radiotherapy or bone marrow infiltration by tumour cells, treatment with rIL-3 leads to a clinically significant restoration of haematopoiesis, especially of thrombopoiesis and granulopoiesis. Adverse effects of rIL-3 are minor at therapeutic doses and include fever, bone pain, headache, and neck stiffness[67]. Recombinant human IL-3 is a multilineage haematopoietic cytokine with promising effects on platelet and neutrophil count augmentation in patients with advanced malignancy.

Interleukin 4

IL-4 is a T cell-derived glycoprotein of molecular weight 20 kDa that was originally characterized as 'B cell stimulatory factor 1'[69]. It was initially discovered as a result of experiments by Howard *et al.* demonstrating its proliferative effects on small B cell subset proliferation[70]. Human IL-4 has also been cloned. It is a 129 amino acid glycoprotein secreted primarily by activated T cells that acts on T and B lymphocytes, monocytes, polymorphonuclear cells, fibroblasts and endothelial cells.

Antineoplastic functions of IL-4 include enhancement of B cell[70], T cell[71], NK cell[72] and mononuclear phagocyte[73] proliferation. IL-4 can also enhance the generation of cytotoxic T cells, mediate induction of LAK cells and synergize with IL-2 in this activity[74]. IL-4 has been shown to inhibit IL-2-induced LAK activity in normal human mononuclear cells[75], but augments LAK activity in mononuclear cells pretreated[76] with IL-2 and such cells derived from IL-2-treated patients with cancer[77]. Furthermore, IL-4 has been shown to stimulate the generation of tumour-infiltrating lymphocytes in human melanoma[72].

Functions on human monocytes and mouse macrophages have also been reported. IL-4 has been shown to increase antigen-presenting ability, surface Ia expression and tumoricidal activity in mouse macrophages[73,78]. It also appears to inhibit TNF, IL-1 and interleukin 6 (IL-6) release[79]. However, effects on respiratory burst activity are conflicting[80].

IL-4 has been demonstrated to have potent antitumour activity by experiments in which a complementary DNA for IL-4 was introduced into the J558 murine melanoma cell line[81]. IL-4-producing J558 cells fail to form tumours in mice and block tumour formation by a variety of other transplantable tumour lines when these cells are cocultured with IL-4-producing J558 cells. The effects of the transfected J558 cells can be inhibited by treating the recipient mouse with anti-IL-4 antibody Forni *et al.* have reported that repeated injections of small amounts of IL-4 into draining lymph nodes can limit the growth of cells of several transplantable tumours[82].

The mechanism by which IL-4 limits tumour cell growth has not been completely established. Tepper *et al.*[81] reported that IL-4 failed to block the *in vitro* growth of transfected J558 cells, indicating that it was not directly toxic to them. They showed that the IL-4-producing J558 cells failed to grow in *nu/nu* mice, suggesting that T cell immunity was not essential for the elimination of the transplanted cells. Redmond *et al.* have demonstrated a beneficial role for IL-4 in upregulating macrophage and T cell cytotoxicity directed against the Lewis lung carcinoma[83].

IL-4-transfected tumour cells have been used to demonstrate the potential of lymphokine gene-transfected tumour cells as a method of cancer therapy[84]. When cells from a spontaneously arising murine renal cell tumour were engineered to secrete large doses of IL-4 locally, they were rejected in a predominantly T cell-independent manner. However, animals that rejected the IL-4-transfected tumours developed T cell-dependent systemic immunity to the parental tumour. This systemic immunity was tumour specific and mediated primarily by CD8$^+$ T cells. Established parental tumours could be cured by the systemic immune response generated by injection of the genetically engineered tumours[84].

The role of IL-4 as an antitumour agent, particularly against spontaneous tumours, remains to be more fully elucidated. None the less, these studies suggest that this cytokine may marshal endogenous host responses in a particularly potent way to limit the growth of certain types of tumour.

Interleukin 5

Interleukin 5 (IL-5) has a molecular weight of 18 kDa. It is a product of activated T lymphocytes and is a lineage-specific eosinophil differentiation and activation factor[85]. IL-5 acts as a costimulator for the growth of antigen-activated mouse B cells and was previously called either 'B cell growth factor 2' or 'T cell replacing factor'.

Murine IL-5 induces eosinophil colonies in human liquid bone marrow cultures and the antibody-mediated killing of tumour cells by peripheral blood eosinophils. It also enhances phagocytosis of serum-opsonized yeast cells by eosinophils[86]. A definitive role for IL-5 as an antineoplastic agent awaits evaluation.

Interleukin 6

IL-6 was initially described as 'β2-interferon' and is also known as 'B cell differentiation factor' and 'hepatocyte-stimulating factor'. It is a 19–26-kDa protein produced by a variety of cells including mononuclear phagocytes, fibroblasts, keratinocytes and endothelial cells[87]. IL-6 is released in response to endotoxin (lipopolysaccharide) and appears to be regulated by IL-1 and TNF. It is released into the circulation in response to injury[88]; its principal functions include stimulation of B cells for immunoglobulin production, promotion of the synthesis of numerous acute-phase proteins and pyrogenic activity by increasing the production of prostaglandins[89].

IL-6 has been shown to augment the growth of freshly isolated human myeloma cells, and the cells constitutively produce IL-6 and express IL-6 receptors[90]. Moreover, anti-IL-6 antibody can inhibit the *in vitro* growth of the myeloma cells[90]. This is direct evidence that an autocrine loop is operating in freshly isolated myeloma cells, and that constitutive production of IL-6 and activation of the IL-6 gene could be involved in the oncogenesis of human myeloma.

Mulé *et al.* have shown that IL-6 has antitumour activity when administered to tumour-bearing mice. Purified human rIL-6 administered to tumour-bearing mice at relatively high doses (33 μg per day) caused substantial reductions in the number of pulmonary and hepatic micrometastases. The dose regimen used was comparable to therapeutic levels of IL-2. Unlike IL-2, IL-6 injections resulted in neither observable toxicity nor death of the treated mice at the doses used[91]. To date, no human studies have been carried out to evaluate the potential antineoplastic effects of IL-6.

Interferons

The interferons are a family of regulatory glycoproteins produced by many cell types in response to viral infections, double-stranded RNA, endotoxin (lipopolysaccharide) and a variety of mitogenic and antigenic stimuli. Human and murine interferons have recently been reclassified as IFN-α, IFN-β (previously type I leucocyte and fibroblast respectively), and IFN-γ (previously type II, or 'immune' interferon). There are heterogeneities within these groups and considerable species specificity.

IFN-α has produced some remarkable results in hairy cell leukaemia[92] and in the carcinoid syndrome[93], but has failed to be of benefit in secondary disease from breast cancer, malignant melanoma and colorectal cancer[94,95]. A response rate of 15 per cent has been observed in patients with advanced renal cell carcinoma treated with IFN-α[96]

Phase II studies of high-dose IFN-α in patients with advanced colorectal carcinoma have not demonstrated any therapeutic responses[94,97]. However, *in vitro* studies have shown that IFN-α synergistically augments the cytotoxic effects of 5-fluorouracil (5-FU) against two human colonic cancer cell lines[98]. A total of 32 patients with previously untreated irresectable colorectal carcinoma received 5-FU $750\ \mathrm{mg\ m^{-2}}$ daily for 5 days by continuous infusion followed by weekly bolus therapy. IFN-α was administered subcutaneously three times a week A 63 per cent partial response rate was achieved, compared with rates of 15–35 per cent with single-agent 5-FU therapy. These findings are encouraging, but proof of superiority over single-agent 5-FU requires controlled clinical trials, currently in progress[98,99] The chemotherapeutic agent dacarbazine exhibits activity against metastatic melanoma. When the combination of IFN-α and dacarbazine was evaluated in a pilot study of 44 patients, a 30 per cent response rate was demonstrated. These results, however, remain to be confirmed in a controlled clinical trial[100].

Both murine and human IFN-γ exert their biological effects through specific saturable binding to a single class of high-affinity receptors These receptors can be found in a number of different tissues including myelomonocytic cells, lymphoid cells, mast cells, endothelial cells, fibroblasts, neuronal cells and melanocytes[101]. Other than its antiviral activity, IFN-γ has been shown to inhibit cell growth in the presence of lymphotoxin (TNF-β)[101] and to induce MHC class I and II expression in target tissues[102–105]. IFN-γ is a cofactor in the activation of macrophages for tumour killing and enhances NK-cytotoxicity[101,106]. It plays an important role in B cell differentiation and has been shown to induce and enhance immunoglobulin secretion in resting B lymphocytes[107–109]. IFN-γ may prove to have clinically significant antineoplastic effects; it may also prove effective in the treatment of a variety of autoimmune diseases. For example, recent data suggest that it may be used to ameliorate some of the symptoms of rheumatoid and psoriatic arthritis[110].

Tumour necrosis factor

TNF is a proinflammatory cytokine that derives its name from its ability to induce necrosis in experimental animal tumours[111]. It is identical to 'cachectin' and was initially isolated during studies aimed at defining the underlying mechanisms of cancer cachexia[112]. It is produced primarily by mononuclear phagocytes in response to endotoxin (lipopolysaccharide)[113]. TNF is initially produced as an inactive propeptide and in active form is a polypeptide existing in multimers of two, three or five subunits.

There appear to be two forms of TNF, one of which (TNF-α or cachectin) is a cytotoxic factor with a molecular weight of 17 kDa released by macrophages following their activation by bacterial endotoxin (lipopolysaccharide)[112]. TNF-β, also known as 'lymphotoxin'[114], has a molecular weight of 18 kDa and is released from stimulated lymphocytes. Both forms have been produced by recombinant DNA technology and appear to have antiproliferative, cytostatic and cytolytic effects against human tumour cells either *in vitro*[115,116] or when injected into nude mice[117]. Human recombinant TNF-α also enhances the cytolytic activity of NK cells[118] and so may theoretically mediate tumour regression through this mechanism Preliminary reports on the clinical administration of recombinant TNF-α do not indicate significant therapeutic effects and describe considerable toxicity[119]. Although initial phase I and II studies using TNF in humans have shown the expected toxicity, few antitumour effects have been observed[119]. However, a role for TNF in cancer therapy may exist when used in combination with either biological or chemotherapeutic agents. The combination of TNF-α with other biological response modifiers such as IFN-γ has theoretical advantages and appears greatly to augment TNF-mediated tumour regression in human breast and colonic cancers implanted into nude mice[120]. However, clinical trials of IFN-γ and TNF have been abandoned because of serious toxicity problems, emphasizing that toxicity from cytokines remains a major factor in limiting their use in immunotherapy.

Colony-stimulating factors

The colony-stimulating factors are a group of glycoproteins with the ability to control the proliferation and differentiation of granulocytes, mononuclear phagocytes and certain related haematopoietic cells. They include IL-3 (multi-colony-stimulating factor), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF)

M-CSF is produced by monocytes, fibroblasts and endothelial cells, and stimulates the formation of macrophage colonies[65]. G-CSF is a product of monocytes and fibroblasts that acts directly on target progenitors to induce the formation of granulocyte colonies *in vitro*[121,122]. GM-CSF is a glycoprotein secreted by activated T cells, endothelial cells, fibroblasts and macrophages[123]. This cytokine provides an effective proliferative stimulus in human marrow cultures to granulocyte, macrophage and eosinophil colonies. It is also capable of stimulating antibody-dependent cytolysis of tumour cells by mature human neutrophils and eosinophils[124]. An important pathway in antitumour defence may be provided by GM-CSF as it induces macrophage tumoricidal activity[125]. *In vivo* administration of GM-CSF decreases tumour growth in a murine Lewis lung carcinoma model[126].

Both GM-CSF and G-CSF are significantly beneficial in the treatment of leucopenia[127,128]. Studies in monkeys show that combined administration of GM-CSF and IL-3 dramatically increases circulating leucocyte levels. Furthermore, phase I and II clinical trials currently underway indicate that GM-CSF may be effective in accelerating the recovery of patients with leukaemia following autologous bone marrow transplantation[129]. GM-CSF is of benefit to patients with myelodysplastic syndrome[130] and it has been observed that neutropenic patients with acquired immune deficiency syndrome receiving daily doses for 14 days exhibit marked leucocytosis[131]. Furthermore, patients with inoperable metastatic sarcomas receiving doxorubicin, ifosfamide and dacarbazine experienced a reduction in the duration and degree of neutropenia when treated with GM-CSF[127].

Similarly, G-CSF seems to shorten the period of neutropenia associated with chemotherapy in animals and humans. Monkeys treated with G-CSF exhibited a dose-dependent increase in leucocyte count, and the duration of granulocyte recovery in phosphamide-treated groups was considerably shortened[132]. Patients with transitional cell carcinoma of the bladder, treated with methotrexate, vinblastine, doxorubicin and cisplatin experienced up to a fourfold increase in neutrophil count on administration of G-CSF, with little or no toxicity observed[133]. In contrast, purified human urinary M-CSF given to leucopenic patients produced only modest effects on circulating leucocyte levels[134]. However, M-CSF may act to enhance monocyte function[135] and may yet prove to be of some therapeutic benefit.

Other cytokines

Other interleukins, such as interleukin 7, interleukin 8 (IL-8), interleukin 9, interleukin 10 and interleukin 11, have not been studied for specific antitumour activity[136]; their role in cancer immunotherapy awaits further evaluation. However, caution is needed in suggesting that all these may be useful in tumour-bearing patients; in some instances cytokines may actually harm patients IL-8 has been characterized as a neutrophil-activating protein; its intravenous injection in rabbits leads to immediate and profound neutrophilia[137] The potential of these cytokines to induce cancers by their effects on cellular proliferation must be addressed carefully.

Natural killer cell stimulatory factor (NKSF) is a recently discovered cytokine purified from the supernatant of an Epstein–Barr virus-transformed B lymphoblastoid cell line (RPMI 8866). It has been examined for its effect on NK- and antibody-dependent cellular cytotoxicity of human colon adenocarcinoma cell lines[138]. NKSF significantly enhanced NK cytolysis of colonic carcinoma and NK-resistant lymphoma cell lines, and on a molar basis was approximately 300 times more potent than IL-2 in generating NK cytotoxicity. Furthermore, NKSF significantly augmented lymphocyte-mediated antibody-dependent cellular cytotoxicity against colonic carcinoma targets, and the combination of NKSF with the antibody CO17-1A had an additive effect on lymphocyte tumoricidal capacity. Thus, NKSF may have a potential role in the treatment of colonic cancer[138].

Conclusions

Knowledge of cytokines and their precise physiological and therapeutic roles is still in its infancy, but understanding of their function is expanding rapidly. At present the role of many cytokines in tumour immunology is still being evaluated in animal models

One of the more interesting developments in the use of cytokines in cancer therapy is 'adoptive immunotherapy' or cell-transfer therapy. Cells of the immune system are removed from a patient and their native cytotoxic activity enhanced *in vitro* by challenge with a cytokine (usually IL-2). The cells are then returned to the patient in combination with the cytokine[18,139]. Tumour-infiltrating lymphocytes require less IL-2 to remain active *in vivo* and the overall dose of IL-2 can be reduced significantly using this method, relieving some of the toxicity of IL-2 therapy.

The possibility of using genetic manipulation to increase the therapeutic potential of adoptive immunotherapy, by introducing genes encoding cytokines such as TNF, IFN-α or IL-2 into tumour-infiltrating lymphocytes, has recently been addressed. Rosenberg *et al.* have undertaken gene transfer therapy in humans. Using retroviral gene transduction they have introduced a marker, the bacterial neomycin resistance gene, into human tumour-infiltrating lymphocytes[140]. Following administration of the 'engineered' lymphocytes to a group of patients with metastatic melanoma, neomycin-resistant cells were present in the circulation and could be recovered from tumour biopsies for up to 2 months with no apparent adverse effects of genetic manipulation[140]. Immunotherapy with genetically engineered lymphocytes would allow delivery of significant amounts of cytokine directly to the microenvironment of the tumour Clinical trials of such cells, genetically engineered to produce TNF, have begun at the US National Cancer Institute[141]. More recent attempts at using genetic manipulation to increase the therapeutic potential of adoptive immunotherapy include the use of gene-transfected tumour cells[84]. Established parental tumours may be cured by the systemic immune response generated by injection of genetically engineered tumours[84]

To date, immunotherapy has not fufilled its initial promise – a realistic inroad into cancer therapy. It remains time consuming and expensive, and further developments will be needed before it can become a commonplace treatment.

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Endotoxin, septic shock and acute lung injury: neutrophils, macrophages and inflammatory mediators

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The treatment of septic shock remains a major problem in surgical practice. Current research on the pathogenesis of the sepsis syndrome focuses on the effects of the lipopolysaccharide constituents of bacterial endotoxin. Evidence suggests that endotoxin induces a whole-body inflammatory response that in turn mediates organ damage, eventually leading to multiorgan failure. The first organ in which failure is usually apparent is the lung, with the appearance of non-cardiogenic pulmonary oedema as part of the adult respiratory distress syndrome. Inflammatory cells involved in lung injury include neutrophils and macrophages, which release mediators such as elastase, oxygen radicals and cytokines. This review summarizes current experimental work on how endotoxin leads to lung injury, based on its effects in animals and patients. Present knowledge suggests that future treatment of septic shock might involve inhibiting the body's inflammatory response to endotoxin. Possible ways of doing this are discussed.

Joseph Lister in 1867 revolutionized operative surgery by publishing the use of carbolic acid to cleanse wounds[1]. The reduction of infection that resulted dramatically reduced the customary mortality rate from trauma. Eighty years later the introduction of antibiotics enabled many of those infections that still developed to be controlled. However, one particular type of infection, Gram-negative septicaemia, still eludes effective therapy and may actually be aggravated by antibiotics. In this condition, if shock is present, the mortality rate continues to be unacceptably high at around 50 per cent despite antibiotics and intensive therapy[2]. The present problem is complex. Dying Gram-negative bacteria shed cell wall components known as endotoxin into the circulation. Endotoxin induces a number of inflammatory mediators in the host that may cause what appears to be progressive and uncontrolled whole-body inflammation. The result is generalized endothelial injury manifest in the lungs as the adult respiratory distress syndrome (ARDS), with pulmonary oedema, decreased lung compliance and arterial hypoxaemia in the presence of a normal pulmonary arterial occlusion pressure[3]. The source of endotoxaemia may be clinically obvious; in cases where it is not apparent it is thought that endotoxaemia may occur in association with injury and hypoxia of the intestinal mucosa. This could, in theory, lead to translocation of Gram-negative microorganisms into the systemic circulation with the consequences described here[4].

The lungs appear particularly sensitive to the effects of insults such as endotoxin. In a 1983 review of patients who died after admission to hospital with multiple trauma, it was found that not only was progressive organ failure the commonest cause of death, but that the first organ to fail was usually the lung[5]. Others have reported similarly and have found direct evidence of a generalized inflammatory response affecting multiple organs in patients who died from sepsis[6]. If the lung injury seen in sepsis could be treated, the familiar progression into multiorgan failure might be prevented. Knowledge of the cellular and mediator effects of endotoxin suggests several ways in which this could be achieved.

Endotoxin activates neutrophils

Endotoxin is probably important in sepsis-associated ARDS since injection into animals induces acute non-cardiogenic pulmonary oedema and lung permeability, mimicking the findings in man In humans, the presence of endotoxaemia correlates with the subsequent development of ARDS[7]. Furthermore, infusion of a monoclonal antibody against endotoxin reduces mortality from Gram-negative sepsis in patients, halving the mortality rate in septic shock[8]. The process by which endotoxin induces ARDS is suggested by the observation that the lungs of animals injected with endotoxin become infiltrated with neutrophils. These cells are probably directly responsible for the resulting damage since in most animal models their selective depletion beforehand prevents the lung injury that would normally result from endotoxin injection[9]. The mechanism by which neutrophils induce injury is indicated by *in vitro* studies showing that endotoxin directly and potently activates neutrophils to produce elastase[10] and superoxide ions[11]. *In vitro* and *in vivo* data indicate that activated neutrophils are capable of inflicting considerable endothelial injury via combined action of these agents, probably acting synergistically[12] (*Figure 1*). Neutrophils incubated with endotoxin are capable of causing acute lung injury when reinjected into animals[13]. Furthermore, endotoxin primes neutrophils to produce an enhanced respiratory burst in response to a second activating stimulus[14]. This priming effect is demonstrated by the ability of trace amounts of endotoxin to act synergistically in producing lung injury in animals whose neutrophils have been exposed to small amounts of a chemotactic peptide[15]. Injection of either agent alone does not cause lung injury in this model, demonstrating that sublethal doses of endotoxin can still provoke significant injury in the presence of other predisposing factors.

Occasional reports of ARDS occurring in neutropenic patients[16,17] imply a neutrophil-independent mechanism(s). Certainly, endotoxin can produce lung injury independently of neutrophils. The mechanism(s) by which it may do so is

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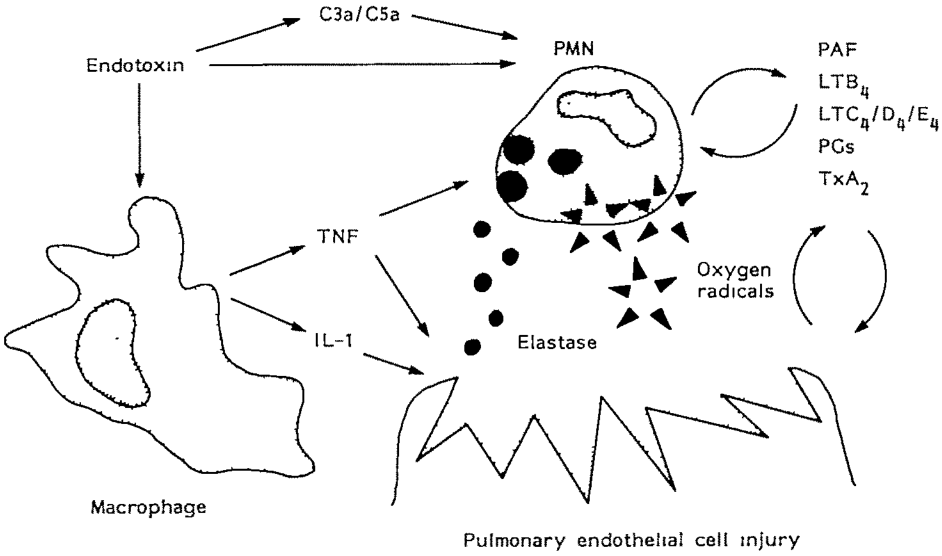

Figure 1 *Proposed mechanism for endotoxin-induced lung injury. Endotoxin either directly or through macrophage products activates polymorphonuclear neutrophils (PMN), which then stick to susceptible endothelial cells Neutrophils injure pulmonary endothelium via release of elastase and oxygen radicals For clarity, several positive and negative feedback loops are omitted TNF, tumour necrosis factor, IL-1, interleukin 1; PAF, platelet-activating factor, LT, leukotriene, Tx, thromboxane, PG, prostaglandin, C, complement*

ill-defined but it could be by direct action on endothelium[18]. Despite this, in most patient with ARDS the lungs become full of activated neutrophils with enhanced proteolytic[19] and oxidative[20] activity. Moreover, the number of neutrophils recovered by bronchoalveolar lavage predicts abnormalities of gas exchange and lung permeability in humans It is therefore likely that neutrophils actively participate in injuring the lungs in human ARDS since most patients so affected are not neutropenic.

Macrophage activation induces cytokines

Despite the potent effects of endotoxin on neutrophils, the initial effector cell of endotoxin-induced organ injury is probably the tissue macrophage. This cell produces many inflammatory mediators and responds to endotoxin[21,22] by quickly producing large amounts of tumour necrosis factor (TNF) and interleukin (IL) 1. TNF has been considered a central mediator of septic shock since the observation in 1985 that a polyclonal neutralizing serum to TNF-α was highly effective in preventing death from endotoxin in mice[23]. In 1987 these findings were confirmed and extended by the observation that a monoclonal antibody to TNF effectively prevented death after bacteraemia in primates[24]. Several other lines of evidence support a central role for this cytokine in mediating septic shock[25]. Injection of TNF reproduces septic shock and causes pulmonary oedema and permeability associated with lung sequestration of neutrophils[26]. C$_3$H/HeJ mice, which cannot synthesize TNF, are resistant to the deleterious effects of injected endotoxin[27]. In humans, injection of endotoxin elicits TNF[28] and the finding of this cytokine in bronchoalveolar lavage fluid predicts mortality associated with ARDS[29].

Since the injection of TNF into animals mimics the effects of endotoxin it is perhaps not surprising that this cytokine induces lung injury via neutrophiils[30], although, as for endotoxin, the lung injury is in some models neutrophil independent[31]. Neutrophils exposed to TNF produce elastase[10], superoxide ion and hydrogen peroxide[32], and are then capable of lysing endothelium[33]. TNF also promotes neutrophil adhesiveness for endothelium[34]

Intravenous injection of IL-1 also produces shock and acute lung injury with sequestration of neutrophils and permeability oedema[35]. Many of its effects are indistinguishable from those of TNF (with the exception that IL-1 does not activate neutrophils) and the two cytokines are synergistic when injected together. Like TNF, IL-1 is produced by alveolar macrophages in patients with ARDS[36]. Furthermore, an IL-1 receptor antagonist reduces lung injury and protects against mortality from septic shock induced by *Escherichia coli* in rabbits[37]. Both cytokines induce profound hypotension that is preventable with cyclo-oxygenase inhibitors, indicating participation of the arachidonic acid metabolites thromboxanes and prostaglandins in the injury[38,39]. The closeness with which experimental injection of either agent reproduces septic shock provides compelling evidence that TNF and IL-1 are mediators of septic shock and acute lung injury. Another cytokine prominent in the sepsis syndrome, IL-6, does not appear to mediate either the fall in systemic vascular resistance or the lung injury characteristic of septic shock. It is not known whether the newly identified cytokine IL-8, a potent activator and chemotactic agent for neutrophils, has a role in endotoxin lung injury since antagonists for *in vivo* use are not yet available. IL-8 has, however, been shown to be present in bacterial sepsis in primates[40].

Platelet-activating factor, leukotrienes, thromboxane and complement activation

There is evidence that some of the effects of endotoxin may be effected by lipid mediators such as platelet-activating factor (PAF), arachidonic acid metabolites and also complement. *In vitro* studies indicate that arachidonic acid products exert control over the production of TNF and IL-1. PAF, leukotriene B$_4$ (LTB$_4$) and C3a are potent stimuli for production of these cytokines[41–43]. In contrast, prostaglandins, particularly PGE$_2$, can inhibit TNF and IL-1 production *in vitro* by negative feedback[44]. It is not known whether arachidonate metabolites also regulate this process *in vivo*. PGE$_2$ is also partly responsible for TNF and IL-1 toxicity, indicating the complexity of the relationships between these mediators. TNF activates neutrophils to produce PAF[45], LTB$_4$[46] and thromboxane A$_2$[47], each of which by itself induces oxidative activity in neutrophils. Direct injection of PAF reproduces many of the features of septic shock. Furthermore, use of a selective PAF antagonist inhibits the lung injury induced by endotoxin in rats[48]. Moreover, levels of PAF in the blood and lung tissue correlate with the development of lung injury in the same setting. Part of the ability of PAF antagonists to reduce this injury may be related to the effects of this factor on neutrophil adhesion to endothelium.

It is known that LTB$_4$ is generated in the lung in response to endotoxin and is likely to affect neutrophils and/or macrophages locally[49]. Present *in vivo* data do not document a conclusive role for the related peptidoleukotrienes $LTC_4/D_4/E_4$ in the sepsis syndrome In one study, a combined LTD_4/E_4 antagonist effectively maintained haemodynamic stability following endotoxin injection in pigs[50]. However, in a similar study the same antagonist did not improve lung injury[51], whereas a combined LTC_4/D_4 antagonist did[52]. The role of thromboxane A_2 is better defined. This agent causes pulmonary hypertension by vasoconstriction of pulmonary arterioles and is responsible for the pulmonary hypertension (but not permeability) seen after infusion of endotoxin[53]. Endotoxaemia also potently activates complement, which stimulates neutrophils and can by itself induce transient lung injury[54]. Infusion of an antibody directed against complement fraction C5a prevents death after a lethal dose of *E. coli* in primates[55]. C5a has been found in plasma and lung tissue of patients with ARDS[56]. Activated complement also promotes neutrophil adhesion to endothelium[57]. Taken together, these findings indicate that endotoxin is capable of generating other inflammatory mediators from neutrophils, which may amplify the inflammatory response.

Adhesion receptors determine neutrophil binding to endothelium and consequent injury

Endothelium exposed to either TNF or IL-1 is more susceptible to neutrophil-mediated killing[58,59], probably because TNF and IL-1 increase endothelial adhesiveness for neutrophils. *In vitro*, close adhesion between neutrophils and endothelial cells appears to be a prerequisite for neutrophil-mediated injury. Like endotoxin, TNF and IL-1 induce adhesion receptors on the surface of endothelium that facilitate neutrophil binding[60] (*Figure 2*). *In vitro*, endothelial adhesion receptors mediate the injury to endothelium caused by activated neutrophils[61]. These receptors, intercellular adhesion molecule 1 (ICAM-1) and endothelial leucocyte adhesion molecule 1 (ELAM-1), may be important in ARDS as there is now direct evidence that at least one of them (ELAM-1) is induced in the lungs in sepsis[62] Both ICAM-1 and ELAM-1 have been shown to mediate neutrophil adhesion and consequent lung injury in different settings in animal models[63,64]. It is not yet known whether blocking these adhesion receptors with monoclonal antibodies can prevent neutrophil recruitment to the lungs and consequent injury in sepsis. It is also not known whether two other classes of adhesion receptors, neutrophil lectin adhesion molecule 1 and endothelial GMP-140 (CD62), are involved in endotoxin lung injury Neutrophil binding to endothelium is a complex process and it is speculated that several or all of these adhesion receptors influence neutrophil-mediated injury *in vivo*.

It appears that, in addition to endothelium becoming a more adhesive surface for neutrophils, a second stimulus activating neutrophils is necessary to promote injury[65]. PAF, LTB_4, thromboxane A_2 and complement fraction C5a all rapidly increase neutrophil 'stickiness' for endothelium[66,67]. Thus, activated neutrophils and endothelium both become more adherent to each other, increasing the potential for neutrophil-mediated injury Antibodies that block adhesion receptors on neutrophils (the CD18 receptors) protect against pulmonary oedema in Gram-negative sepsis in pigs by preventing the process of neutrophil adhesion to endothelium[68] The CD18 receptor is the neutrophil ligand for endothelial ICAM-1. Further evidence that adhesion is important is that binding of CD18 to endothelium controls the release of hydrogen peroxide into the extracellular space by the neutrophil[69] TNF also stimulates endothelium to synthesize PAF[45,70], which promotes neutrophil adherence to endothelium via mechanisms dependent on endothelium as well as the neutrophil.

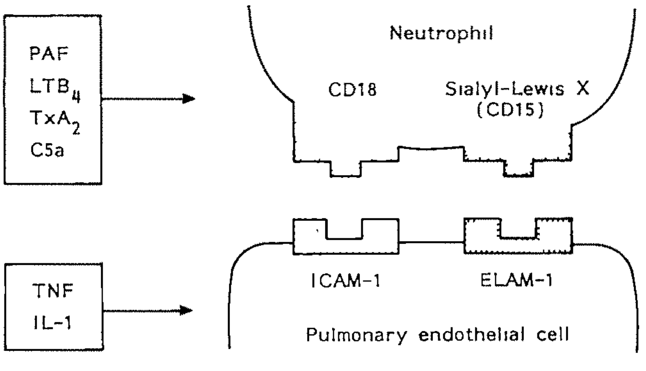

Figure 2 *Putative adhesion receptors in neutrophil-mediated lung injury induced by endotoxin Lipid mediators and complement (C) stimulate neutrophils to adhere to endothelium, which is also stimulated by tumour necrosis factor (TNF) and interleukin 1 (IL-1) to become more adhesive for neutrophils via further adhesion receptors intercellular adhesion molecule (ICAM) and endothelial leucocyte adhesion molecule (ELAM). PAF, platelet-activating factor, LT, leukotriene, Tx, thromboxane*

New approaches to treating septic shock and endotoxin lung injury

Current treatment of endotoxin-induced lung injury and sepsis is supportive, with fluid replacement, antibiotics and artificial ventilation Antibiotics can, however, exacerbate endotoxaemia in severe Gram-negative infection[71] Despite full intensive therapy and conventional pharmacological treatments, the mortality rate from the sepsis syndrome is still considerable.

Future treatment of Gram-negative sepsis and ARDS may be aimed at inhibiting the host's inflammatory response to endotoxin. This could involve preventing neutrophil and macrophage activation, antagonizing cytokines and lipid mediators, or using antiadhesion antibodies to prevent neutrophil-mediated injury. The difficulty in designing such treatments is that inhibition of several of the inflammatory mediators mentioned might be detrimental to the body's normal and appropriate response to injury In particular, this involves guiding neutrophils across the vascular endothelium into tissues to engulf and lyse bacteria This process is controlled partly by the same mediators thought to be responsible for the sepsis–acute lung injury syndrome.

The recent findings of a randomized double-blind controlled trial of a monoclonal antiendotoxin antibody in treating proven Gram-negative septicaemia are encouraging[8]. In a group of patients with Gram-negative septicaemia who were not shocked, 32 of 105 (30 per cent) died within 28 days after treatment with the antibody, compared with 45 of 92 (49 per cent) who were treated with placebo. This reduction in mortality rate was significant ($P = 0{\cdot}014$) Similar results were found in a further group of patients who had shock as well as Gram-negative septicaemia at the start of treatment. This monoclonal antibody is now available and, although expensive, has been found by one independent group to be cost effective[72]. A second randomized double-blind controlled trial of a monoclonal antiendotoxin antibody has been reported[73]. In this study, there was a significant reduction in mortality rate in patients with Gram-negative septicaemia (but not shock) treated with antibody. Eleven of 74 treated patients died in the first 2 weeks of the study compared with 23 of 63 given placebo ($P < 0{\cdot}01$). By 30 days the mortalities were 30 of 74 treated patients compared with 43 of 63 receiving placebo.

Several differences in outcome between these two important studies have aroused critical comment, the main discrepancy being that in the former there was a reduction in mortality rate in patients with Gram-negative septicaemia who were shocked on entry into the trial, whereas in the latter, treatment did not alter the mortality rate in similar patients[74]. These differences may reflect the source of the monoclonal antibodies used: in the first trial the antibody was human, in the second it was murine. It is postulated that murine antibodies are unable to duplicate precisely the functions of human antibodies in man. A third study provides support for antiendotoxin therapy benefiting patients with endotoxaemia and septic shock[75]. In this uncontrolled trial, polyclonal immunoglobulin reduced the mortality rate, one of 27 treated patients dying within 28 days of treatment compared with nine of 28 in the untreated group ($P < 0{\cdot}01$).

Differences in the selection criteria used for each group of patients, and in the antigenic characteristics of the two monoclonal antibodies and the polyclonal immunoglobulin used, may also explain the different results between these studies[76]. A problem with important financial implications is that there was no overall reduction in mortality rate in the first two studies if every treated patient was included in the results[74]. The argument about whether these agents should be in widespread use is unlikely to be resolved except by further rigorous trials to define which particular group(s) of patients may benefit. Recent data from a patient study suggest that defining the criteria to select these patients is not straightforward. Of 100 patients with clinical signs of septic shock, 57 did not have endotoxaemia, although the presence of endotoxaemia correlated strongly with clinical signs of sepsis and poor outcome[77]. Moreover, only 26 per cent of the patients with septic shock and endotoxaemia had Gram-negative septicaemia on blood culture. Conversely, not all patients with proven Gram-negative septicaemia had endotoxaemia. Current opinion favours use of these antibodies only for patients who strictly fulfil the entry criteria used in the trials with monoclonal antibodies discussed above[76].

A phase 1 trial of an anti-TNF monoclonal antibody in sepsis has been published[78]. In this study, 14 patients with septic shock and APACHE II scores of 20 or greater were treated with the antibody. Although there was no reduction in mortality rate in this group of severely ill patients, mean arterial pressures rose on average and at 24 h this rise was significant ($P = 0{\cdot}013$). Phase 3 trials of TNF monoclonal antibody in sepsis are ongoing and their results keenly awaited.

Steroids have not been beneficial in Gram-negative septicaemia[79]. The reason for this is suggested by the observation that the messenger RNA for TNF is induced in cultured macrophages within a few minutes of exposure to endotoxin. Treatment with dexamethasone is effective in preventing messenger RNA expression and thus TNF production, but only if given at or before the time of endotoxin administration. If dexamethasone is given 20 min after endotoxin challenge, the macrophage TNF response is not prevented[80].

There have been no large trials to date of agents that selectively inhibit the various lipid mediators described above and it might be expected that antagonists to these would be beneficial. In a preliminary study it was found that ibuprofen did improve oxygenation in some patients with ARDS[81]. In a trial of infusion of PGE_1 in patients with ARDS there was an improvement in oxygen delivery to the tissues although this was not associated with an increase in survival[82].

Treatment in animals with antiadhesion antibodies, such as those directed against the CD18 receptor, may not be immediately applicable to humans. Neutrophils use CD18 to phagocytose bacteria[34] and, if this is made defective by the use of anti-CD18 antibodies, there may be increased susceptibility to infection. In preliminary studies this has indeed been found to be the case after subcutaneous injection of *Staphylococcus aureus* in rabbits[83]. This finding highlights the theoretical drawback of anti-inflammatory therapy.

In patients with trauma, treatment with human recombinant superoxide dismutase reduces morbidity, demonstrating the importance of the superoxide ion[84], and it is possible that use of this or other antioxidants will become routine in patients with sepsis. A preliminary report of a randomized double-blind trial of *N*-acetylcysteine in patients with established sepsis-induced ARDS suggests that this antioxidant is useful[85]. Specific inhibitors of neutrophil activation may also be of benefit. For example, pentoxifylline is effective in reducing endotoxin lung injury in dogs[86]. Finally, a recent report indicates that levels of the potent vasodilator nitric oxide are raised in patients with sepsis and its presence correlates with the fall in systemic vascular resistance characteristic of septic shock[87]. Although it is not known whether nitric oxide is ultimately responsible for the systemic hypotension in septic shock, it is conceivable that future treatments might involve inhibiting this agent.

There is then, at last, some hope for patients seriously ill with Gram-negative septicaemia, but much has still to be learned. The extent to which the experimental findings presented here will lead to effective treatments remains to be seen.

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The electronic information revolution and how to exploit it

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Medical information is increasingly stored in electronic format, enabling faster and more flexible access to the literature. Online, compact disc and floppy disc databases are widely available. The origins and development of these different database media are described. The strengths and weaknesses of each, and the ways in which they complement each other, are examined. Ease of access to medical information can result in data management problems; the role of bibliographic software in ensuring full exploitation of the electronic information revolution is therefore emphasized.

The medical literature has grown rapidly since the publication of the first annual volume of *Index Medicus*, which recorded 20 000 articles in 1879. One hundred years later this total had increased more than tenfold to around 250 000 annually[1]. The *MEDLINE* database, which offers access to *Index Medicus* by computer, extends its coverage of the literature back to 1966. Between 1971 and 1984 its size increased from 147 000 to more than 4·5 million references, while the full set of 21 databases produced by the US National Library of Medicine (NLM) at the end of 1984 contained over 8·5 million references between them[2]. The current annual growth rate of the *MEDLINE* database is over 300 000 references.

There have been many methods for handling this flow of information. Until the mid-1980s various systems for filing and retrieving reprints were described. Some were based on the chapter headings and index of a major medical textbook[3,4]. Some used individual classifications[5,6] while others employed a card index system[7,8]. However, manual retrieval systems were inadequate when a personal reference collection extended beyond 200 items[9,10], and some form of automation was needed. This proved to be a major exercise and involved using both mainframes[9,11–13] and microcomputers[10,14–21]. The creation and maintenance of databases required considerable programming skill and time. Alagesan and McLeod reported that their program took 'some hundreds of weeks' to develop[19], while Schmid and Böhmer invested 'an enormous amount of time' in 'editing and adding each individual article to a literature data base'[20].

Despite these efforts many doctors continued to have difficulty in managing their information. A survey of physicians[22] in 1985 found that one-third had no organized method for storing and retrieving journal articles and half were dissatisfied with the organization of their journals. It was concluded that more efficient access to printed information was needed, preferably via a desktop computer offering easy retrieval of specific points of required information. At the time this was considered to be 'over the horizon'. However, with the advent of easily accessible databases of information stored on compact disc and the development of powerful and affordable commercial database software for managing personal reprint collections, opportunities for fast and efficient retrieval and organization of medical information were imminent.

This article describes the origins and development of these innovations and reviews what is currently available in terms of databases and bibliographic software.

Electronic information sources

Online databases

The present ease of access to massive quantities of the world's medical literature in electronic format has its origins over 30 years ago when, to enable faster processing of the increasing volume of published literature, the US NLM undertook the development of a computerized system for the production of the printed *Index Medicus*[23,24]. The system was called *MEDLARS* (Medical Literature Analysis and Retrieval System) and the first issue of *Index Medicus* to be produced by it appeared in August 1964. The versatility of the system was rapidly appreciated since it could be used to generate listings of information on specific topics to meet individual needs. The ability to search for complex combinations of terms gave it a major advantage over any printed index. As a result the *MEDLARS* demand search service was initiated to meet requests from health professionals for bibliographies. This service proved popular and demand reached a peak in 1970 when 24 000 searches of the database were processed on 21 computers at centres based in the USA and eight other countries[25].

In 1970 the turnaround time for *MEDLARS* search requests in the USA was estimated[23] at 40–60 days. This was inadequate to meet urgent needs. To enable faster access from a wider range of organizations the database, renamed *MEDLINE*, was made available 'online' in the USA over a national telecommunications network on 29 October 1971. Access from outside the USA was developed subsequently. The number of *MEDLINE* searches processed in October 1972 alone was 10 605, giving an estimated annual rate[25] of 140 000 per year. This figure rose by 1980 to 1·5 million searches of the NLM's 19 databases from more than 1000 organizations worldwide[23]. At this time developments in telecommunications networks and the entry of a diversity of companies into the database industry[26–29] led to the establishment of online access to 400 databases[30] in a wide range of subject areas. Today there are more than 5000 databases[30], medicine is prominently represented with more than 200 databases listed in the *Directory of Online Healthcare Databases*[31]. The compilers of this directory estimate that these databases in 1989 contained 50 million references from 100 000 international source publications. Although *MEDLINE*, which indexes more than 3000 journals, remains the best known online database, there are many other important sources which offer varied routes of access to medical information[30,32–37]. Most are categorized as

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Table 1 *Examples of online databases*

Name	Coverage	Information provider	Update frequency
BIOSIS	Life sciences literature	BIOSIS	Twice monthly
BMA Press Cuttings	Medical topics reported in any of 30 newspapers	British Medical Association	Daily
CANCERLIT	Clinical and experimental oncology	US National Library of Medicine	Monthly
Comprehensive Core Medical Library	Full text of more than 70 medical journals (e.g *Br J Surg*, *Ann Surg*), yearbooks and textbooks	BRS Information Technologies	Twice weekly
EMBASE	Most medical subjects, especially drug information, from 3500 journals	Elsevier Science Publishers	Weekly
Health Planning and Administration	Healthcare planning and management	US National Library of Medicine	Monthly
MEDLINE	Most medical subjects from 3000 journals	US National Library of Medicine	Weekly
SCISEARCH	Citation records for individual authors and papers	Institute for Scientific Information	Weekly
SPORT	Sports medicine	Sport Information Resource Centre	Monthly

bibliographic databases, characterized by the provision of full citations to the literature, usually with abstracts but not the full text of the original publications. One of these is *EMBASE*, corresponding to the printed *Excerpta Medica* series, which indexes a total of 3500 journals with particular strength in drug information. Others offer more focused access to individual specialities such as acquired immune deficiency syndrome (AIDS), cancer, alcoholism, toxicology, mental health, ageing, sports medicine, medical ethics and health administration. Some of these are summarized in *Table 1*.

Some databases do contain the full text of a number of publications. The *Comprehensive Core Medical Library*[38] brings together in electronic format the whole text of more than 70 journals, 30 yearbooks and 15 textbooks. These include *The British Journal of Surgery* (from May 1986), *The American Journal of Surgery* (from February 1986) and *Annals of Surgery* (from February 1985). Other full-text databases include information on cancer treatment protocols, drug effects, hazardous substances, and equipment and materials for diagnostic and therapeutic purposes.

Unfortunately, the use of online databases can be expensive and complicated, preventing their benefits from reaching more than a limited number of users. Charges are levied according to length of time of connection to a database and the number of references printed These costs vary but, despite some subsidy from government sources for medical databases, one estimate puts the average total expenditure for database use at US $100 (over £50) per h at 1985 rates[2].

Technically, the process of accessing and searching online databases can be complicated. Connection to a host computer over a telecommunications network is a multistage operation, involving special protocols and command languages that vary from one system to another Furthermore, effective searching of databases requires a thorough knowledge of their individual indexing systems Different databases use different keyword systems, for example the NLM's Medical Subject Headings (MeSH), and apply them according to different principles[39]. For these reasons it has not been common for medical personnel to conduct online database searches for themselves. They remain largely the preserve of librarians or information scientists who are fully trained in the appropriate techniques, thus ensuring that efficient searches can be conducted at minimum cost.

The NLM has led the way in overcoming the technical barriers through the development of two 'front-end' systems, PaperChase[39–43] and Grateful Med[24,39,44–47], although others too have tried to attract end users to do their own searching[2,48]. Front-end software is so called because its role is to provide a simpler interface between system and searcher than that offered by command languages. It guides the searcher through the retrieval process by offering screen menus and accepting natural language. PaperChase and Grateful Med are menu driven, tolerate spelling mistakes or deviations from the required syntax for entering author or journal names, and interact with the searcher to suggest better retrieval strategies, using appropriate terms from the Medical Subject Headings.

Cost, however, remains a problem; in many institutions the option of having a librarian or information scientist perform online searches remains cheaper. Despite more enlightened approaches from companies in the data industry, which base costs mainly on the data retrieved rather than the time taken for the search, the most significant development in making electronic information retrieval facilities easily accessible in a cost-effective way to a wider user group has been the advent of the compact disc as a medium for data distribution.

CD–ROM databases

CD–ROM (compact disc–read only memory) is one of a number of compact disc formats A CD–ROM disc is 'read only' in the sense that the user can only read data from it, never add to it. The compact disc was introduced by the Philips and Sony companies in 1980, offering a medium capable of mass storage of recorded data despite its small size (12 cm in diameter with a thickness of 1·2 mm). Data are recorded on to the disc in digital form using a laser beam[49–51]. Compact discs were best known at first for audio storage, their exceptionally high-quality reproduction of original sound having an immediate impact on the music industry Subsequent development of the technologies involved has produced its own literature[29]. CD–ROM, which is one of these technologies, takes advantage of the ability of the compact disc to store vast quantities of text, estimated at the equivalent of 250 000 pages, 100 copies of *Harrison's Principles of Internal Medicine*[52], or in computer terms 600 megabytes.

At last the quantity of information contained in medical databases such as *MEDLINE* (which needed the kind of storage space previously only offered by large mainframe computers such as those of the NLM in Bethesda, Maryland, DIALOG Information Services in Palo Alto, California, or Data-Star in Berne, Switzerland) could be brought inside organizations and searched locally. The first CD–ROM databases were marketed in 1985, since when their popularity has increased to the extent that 2212 titles are listed in the 1992 edition of the *CD–ROM Directory*[53] (*Figure 1*).

Two pieces of equipment are essential for searching a CD–ROM database: a microcomputer and a special player or 'drive' to read the data. An interface card installed in the computer and a connecting cable to the drive allow data read from the CD–ROM disc to be displayed on the computer screen. Because all the data are stored locally there is no need to use telecommunications networks. The time taken to perform a search is immaterial since CD–ROM databases are either purchased outright or, more commonly, hired for an annual subscription of £500–2000, thereby allowing unlimited use within an institution at no further cost. Another major advantage is that most CD–ROM systems present easily comprehensible menu interfaces[54] comparable to those of 'front-end' online database software such as PaperChase and Grateful Med described earlier.

Searches of *MEDLINE* on CD–ROM, for instance, can be highly specific since a number of different concepts can be searched and linked, with provision for easy retrieval by author, subject keyword, journal, year of publication or any combination of these. This provides more powerful, comprehensive and flexible retrieval capabilities than the printed *Index Medicus*. Furthermore, once a reference is located an author abstract will usually be available and may contain all the information required[42,47,55]. The searcher will be able to examine each abstract carefully at leisure and at no extra cost. Important references can either be printed out or copied on to a floppy disc for later reading or printing from a microcomputer.

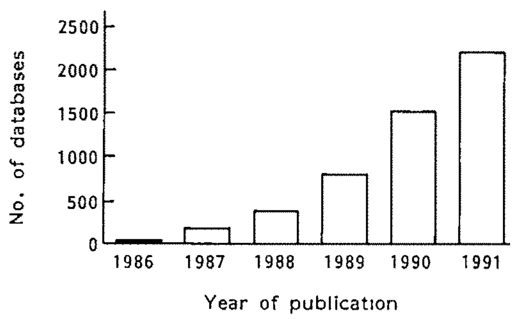

Figure 1 *Growth of compact disc–read only memory databases. Source:* The CD–ROM Directory 1992. *London: TFPL Publishing, 1991*[53]

Table 2 *CD–ROM databases by subject*

Subject	No	Percentage
Biomedicine, health and nursing	187	7·6
General interest, leisure and recreation	172	7·0
Science and technology	168	6·8
Banking, finance and economics	157	6·4
Government information and census data	149	6·0
Business and company information	145	5·9
Computers and computer programs	141	5·7

Source: *The CD–ROM Directory 1991*. London: TFPL Publishing, 1990

Medical subjects have again been in the forefront of this technology and were most prominent in an analysis of the subjects covered by the 1522 databases listed in the 1991 edition of the *CD–ROM Directory* (*Table 2*). *MEDLINE* has again proved to be the most familiar database and has commonly been the first CD–ROM database adopted by medical libraries. Different versions of *MEDLINE* in compact disc format are available[56] and include SilverPlatter, Compact Cambridge, DIALOG OnDisc and CDPlus.

The choice of medical databases is widening all the time (*Table 3*). Bibliographic databases include subsets of the *EMBASE* database (*Excerpta Medica CD*) for fields such as cardiology, obstetrics and gynaecology, gastroenterology and radiology. Among other fields covered by bibliographic CD–ROMs are AIDS, cancer, drug information, health services administration and occupational health.

The use of CD–ROM is expanding and the distribution of full-text information is a growth area. Some databases such as the *AIDS*[57] and *Viral Hepatitis* Compact Libraries contain a mixture of bibliographic and selected full-text information. Others provide the text of whole reference works or journals[58]. These include the *Oxford Textbook of Medicine*[59,60], a series of *Year Books*[61] with subsets for neurosurgery, plastic and vascular surgery. Existing or planned journals on CD–ROM include recent years of *Archives of Surgery*, *Journal of Bone and Joint Surgery*, *New England Journal of Medicine*, *The Lancet*, *Journal of Trauma* and *Critical Care Medicine*. CD–ROM can double as a teaching and learning tool and a product called *CONSULT* includes a library of more than 50 simulated patient management problems in which the student can interact with the computer and work through diagnostic and therapeutic procedures.

Databases on floppy disc

A less heralded but, because of its cheaper subscription rates, even more accessible medium for distributing medical information in electronic format is the ordinary floppy disc[62]. This medium, although lacking the capacity of CD–ROM for mass storage, has proved ideal for distributing bibliographic data from the most important medical journals at weekly intervals. As a result, floppy disc databases have been able to fill a gap left by their CD–ROM counterparts. Their weekly updating schedule and more basic indexing enable them to provide details of papers published 4–6 weeks previously, whereas it can take several months before a paper is included in *MEDLINE* on CD–ROM.

Biomedical updating services available on floppy disc are the *Clinical Medicine* and *Life Sciences* editions of *Current Contents on Diskette*[63–67], *Medical Science Weekly* and *Reference Update*[63,64,68,69] (*Table 4*). Apart from *Clinical Medicine* there are two versions available which differ only according to the number of journals they cover. Thus *Current*

Table 3 *Examples of CD–ROM databases*

Name	Coverage	Information provider	Update frequency
British Medical Journal	Full text of *British Medical Journal* for latest 5 years	British Medical Association	Annually
Compact Library AIDS	Full text of *AIDS Knowledge Base*, journal articles and drug trial reports	Various, including US National Library of Medicine and journal publishers	Quarterly
CONSULT	Complete text of *Scientific American Medicine*; 50 patient management tests	Scientific American Medicine	Quarterly
Excerpta Medica CD	Abstracts of articles on selected areas, e.g. cardiology, gastroenterology	Elsevier Science Publishers	Quarterly
MEDLINE	Abstracts of most articles from 3000 journals	US National Library of Medicine	Monthly
Oxford Textbook of Medicine	Entire text of 2nd edition of *Oxford Textbook of Medicine*	Oxford University Press	Latest edition
Year Books on Disc	Text of volumes in *Year Book* series, including surgery and vascular surgery	Year Book Medical Publishers	Annually

Table 4 *Examples of floppy disc databases*

Name	No. of journals	Annual cost (£)	Information provider	Update frequency
Current Contents on Diskette Clinical Medicine	800	250	Institute for Scientific Information	Weekly
Current Contents on Diskette· Life Sciences	600 or 1200	170 or 250	Institute for Scientific Information	Weekly
Medical Science Weekly	500 or 1000	185 or 295	Elsevier Science Publishers	Weekly
Reference Update	500 or 1000	240 or 300	Research Information Systems	Weekly

Table 5 *Selected personal database software packages*

Name	IBM/Macintosh	Cost (£)	Supplier	General comments
EndNote	Both	115–275	Cherwell Scientific	Fairly easy to use; limited range of medical databases supported for direct data importation
Get-a-Ref	IBM	75–150	DatAid, Sweden	Good user interface with fast searching but can be difficult to generate bibliographies for manuscripts
Papyrus	IBM	60	Research Software Design	Cheap and flexible but search interface is clumsy, generally time-intensive and best for advanced users
Pro-Cite	Both	335–630	Personal Bibliographic Software	Overall market leader very flexible and fairly easy to use; multidisciplinary rather than medical focus
Reference Manager	Both	190–320	Research Information Systems	Medical market leader fast, efficient and easy to use, designed for medical users, offering limited flexibility

Contents on Diskette: Life Sciences is available in both 600- and 1200-journal editions. This is fewer than CD–ROM databases but is still significant; in each case surgery is well represented. These products offer standard retrieval facilities, including the ability to search for information by author, subject or journal name, and are marketed particularly to individual researchers who can use them to run their own searches and view the results either as journal contents pages or bibliographic references. Each of these services costs between £170 and £300 annually and runs on a standard microcomputer with a hard disc. Reprint request cards can be automatically generated, a valuable service when the range of journals held in the nearest medical library is limited.

At the Royal Free Hospital the Medical Library offers its users a weekly current awareness service[70,71] based on *Current Contents on Diskette* for an annual fee of £25, making the service self-funding[72]. The Library is informed by the researcher of a specialized field of interest and performs a weekly search for references matching this subject profile. These are downloaded on to a floppy disc and delivered by internal post or electronic mail, allowing the search requester to scan the results at leisure and store the references of interest.

Online, CD–ROM or floppy disc?

The three different computerized routes to information have their advantages and disadvantages relative to the varying needs of medical personnel It is probable that each will be used at different times to solve different problems One survey[73] has established that CD–ROM searches are more frequently used for routine clinical problems and daily research Online searches are employed more often for major research projects because of the wider range of databases available. Updating services on floppy disc are designed purely for current awareness purposes and will always need to be supplemented by retrieval from online or CD–ROM databases for longer term and more comprehensive results. The important point is that 'nearly anyone in medicine may almost instantaneously gain critical information that was previously difficult to access, wherever and whenever it is needed'[74]

A recent development combining useful features of all three media is the provision of access via the UK Joint Academic Network (JANET) to a number of major databases produced by the Institute for Scientific Information, including the *Science Citation Index*[75]. Searching is free of charge for registered individuals at UK academic institutions which pay a fixed annual subscription charge to the service. The databases are online in the sense that the user connects to them directly through JANET. Their storage is on a mainframe computer at Bath University and allows faster processing of searches than is the case for CD–ROM workstations They offer one of the major advantages of CD–ROM databases, namely the ability to conduct a search in the user's own time without the need to consider cost. In addition they are updated at weekly intervals, emulating the currency of information offered by floppy disc databases. The use of JANET as a vehicle for direct access to major international databases is still embryonic but could become well established in the future if the initial experiment is successful. Negotiations to offer access to *EMBASE* via JANET have recently been successfully concluded[76].

Information management

It is clear that electronic databases have put a vast range of information at the disposal of the medical profession. This increased ease of access can be a mixed blessing since it may result in the retrieval of unmanageable quantities of hitherto unknown information. Difficulties will arise if this information remains unorganized. The results of many searches may be stored in a series of separate files on a number of floppy discs or as multiple printouts dispersed at various locations. The result is likely to be 'information anxiety'[77], an awareness that a piece of information exists but an inability to locate it except perhaps by returning to the library and searching through the database in which it was originally found. This is a time-consuming procedure that can negate the advantages of having easy access to electronic databases. It can be avoided by good information management.

Numerous microcomputer software packages are now available for personal bibliographic database creation and management[78–83]. For medical applications, these include Reference Manager[68,84–87], Pro-Cite[85,88], EndNote[85,89], Papyrus[90,91] and Get-a-Ref[92]. These packages vary in price from around £60 to £630 (*Table 5*) and the range of powerful features that they offer tends to repay the investment quickly. Software of this nature has been developed specifically to cope with the proliferation of information in electronic format and has brought the benefits of computerized information management to a range of users far beyond those with the time and programming skills necessary to develop their own databases. There is a clear advantage in using custom-made software for a specific application, obviating the need for individual or departmentally generated programs which, at great effort, may achieve little more and probably less.

Features of bibliographic software

These packages vary in operating speeds, ease of use and range of features offered. Direct importation of data downloaded from electronic databases, flexible data retrieval and output of references in the different styles required by medical journals are features common to all.

Direct data importation is vital to the efficient use of information retrieved from any of the categories of electronic database. It enables data to be automatically transferred to the database package irrespective of the format employed by the online, CD-ROM or floppy disc database from which they were obtained. The facility to create personal databases containing 20 years of references, often with abstracts, on specialist subjects without the need to enter them personally represents a major saving in time and an intelligent use of the effort expended in compiling and indexing the original database. Two points to note are that most packages will support direct importation from only the more popular databases and that copyright restrictions prevent mass importation of data from any one source (e.g. downloading an entire year's contents from *MEDLINE*) These restrictions should not hamper genuine personal research needs.

Personal bibliographic software also ensures that imported data can be easily searched through a variety of different routes Thus an article can quickly be retrieved if the searcher knows anything significant about it, for example one of its authors, the journal or year in which it was published, or a keyword contained in its title, abstract or subject headings. Good database software brings the power of online or CD-ROM data retrieval to the desktop The personal database can also be used as the basis for organizing a reprint collection of any size In the case of most software packages each reference in the database is automatically assigned a unique identifying number that can be used to file a copy of the original publication.

A major feature of this type of software is the ability to generate lists of references directly from its databases in any of the various styles required for submission of a manuscript to medical journals. Many packages already contain the formats for a wide range of journals and provide the facility for the user to create others easily. Once the format required by the target journal is established, the author's only concern is to decide which references to cite. The better database packages will allow direct interaction between the author's word processor and personal database, enabling reference selection to be performed as the manuscript is written When the manuscript is complete the database software will generate the bibliography to be appended, taking account of any specific journal requirements automatically (e.g. the individual reference layout or the need to use ordinary, bold or italic type). It will also provide the text citations (e g. reference numbers or authors and years) at appropriate points in the main body of the manuscript. These facilities allow the author to concentrate on the subject matter of the text rather than the organization of its references and represent a significant saving of time. This is especially so if a manuscript needs to be submitted to a second journal whose style is different from that of the first, the changes being made automatically by the program once it is informed of the new target journal. As a result it will never be necessary to write out any of the references if they were originally imported from an electronic database such as *MEDLINE*, thus eliminating unnecessary paperwork, reducing potential human error and making the information gathering process more streamlined.

A working combination of electronic information products

This review has described a broad range of electronic information products, a number of which have been used in its composition. The choice of online, CD-ROM and floppy disc databases and of personal database software is wide, and it may be helpful to describe the combination for which the authors have opted.

In gathering information for this article online searches of the *EMBASE* and *BIOSIS* (biosciences) databases were conducted. The JANET network enabled searches to be run on the Institute for Scientific Information's citation databases, providing access to articles in journals related to and outside medicine. CD-ROM was the medium through which the *MEDLINE* database was searched; this was supplemented with an information science database, *Library and Information Science Abstracts* (LISA), also on compact disc. For ongoing current awareness the authors have found the *Current Contents on Diskette* series invaluable, making full use of the updates delivered each week in floppy disc format. The personal database software package, Reference Manager, was the key to keeping control of the amount of information generated by these searches. This software has been designed specifically for use by biomedical researchers and offers the advantages of ease of use, direct importation from the major databases and flexible output of references in the styles required by different journals. As a result it has rarely been necessary to write down any of the references cited or to type them into the personal database. The bibliography was generated with minimal effort, requiring only that the software be instructed to adapt an existing predefined journal style to fit the requirements of *The British Journal of Surgery*.

Conclusion

Technological advances, most notably the application of the compact disc medium for information storage and retrieval, have made the medical literature more accessible, despite its continuing growth. Electronic information sources now provide valuable support for clinical decision making on a regular basis[47,55,93,94]. They enable researchers to establish the presence or otherwise of prior contributions to the literature before undertaking projects or publications[73] These sources also serve a vital function in terms of awareness of recent literature and some libraries have taken the initiative of developing electronic current awareness services whereby updates of articles published on particular subjects of interest to individual researchers are delivered on floppy disc at weekly or monthly intervals[71]. Services of this nature help to alleviate problems of slow dissemination of new medical information[95].

New opportunities have also arisen, through the increased availability of powerful and reasonably priced bibliographic software, for better management of large quantities of information. The establishment of personal bibliographic databases has made it possible to make optimum use of the wide range of medical information available in electronic format and has helped to make the processes of research and publication more efficient. The effort involved in developing new information retrieval and management skills will quickly repay itself in the time saved in rapid location of essential data, effective control of reprint collections, and easy production of manuscript bibliographies The expense involved for an institution or department is minimal when compared with the benefits.

Recent trends have been towards the increased availability of medical information in electronic format, simpler methods for searching databases and an improved ability to store and use the information so derived. Such trends are likely to continue and will make collaboration between hospital or medical school departments and their libraries or information centres all the more important. This will mean that training in the use of databases, to navigate the literature and control the flow of information, is fully available to medical staff and students. Perhaps the best way to be certain that future doctors are adequately trained to exploit these developments is to ensure that undergraduate medical curricula incorporate information technology modules that include details of electronic information sources and personal database management.

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Appendix. Contact information

Online database vendors

Data-Star
Plaza Suite
114 Jermyn Street
London SW1Y 6HJ
UK
Tel. (071) 930 5503
Fax (071) 930 2581

Dialog Information Services
PO Box 188
Oxford OX1 5AX
UK
Tel. (0865) 730275
Fax (0865) 736354

National Library of Medicine
BLAISE Information Services
The British Library
Boston Spa
Wetherby
West Yorkshire LS23 7BQ
UK
Tel (0937) 546585
Fax (0937) 546586

CD-ROM publishers

Cambridge Scientific Abstracts
Microinfo Ltd
PO Box 3
Omega Park
Alton
Hampshire GU34 2PG
UK
Tel (0420) 86848
Fax (0420) 89889

SilverPlatter Information Ltd
10 Barley Mow Passage
Chiswick
London W4 4PH
UK
Tel. (0800) 282133
Fax (081) 995 5159

Dialog OnDisc
PO Box 188
Oxford OX1 5AX
UK
Tel (0865) 730275
Fax (0865) 736354

CD Plus Ltd
1 Lamington Street
London W6 0HU
UK
Tel. (081) 748 3777
Fax (081) 748 2302

Current awareness services on floppy disc

Current Contents on Diskette
Institute for Scientific Information
Brunel Science Park
Brunel University
Uxbridge
Middlesex UB8 3PQ
UK
Tel. (0895) 270016
Fax (0895) 256710

Medical Science Weekly·
Excerpta Medica Publishers BV
Excerpta Medica
Molenwerf 1
1014 AG Amsterdam
The Netherlands
Tel (6) 022 1766
Fax (20) 5803 222

Reference Update·
SilverPlatter Information Ltd
10 Barley Mow Passage
Chiswick
London W4 4PH
UK
Tel. (0800) 282133
Fax (081) 995 5159

Bibliographic software

EndNote:
Cherwell Scientific Publishing Ltd
The Magdalen Centre
Oxford Science Park
Oxford OX4 4GA
UK
Tel. (0865) 784800
Fax (0865) 784801

Get-a-Ref.
Datagen Erlandsson HB
Nordkapsgatan 10
I-164 35 Kista
Sweden
Tel. and fax (08) 750 8718

Papyrus:
Research Software Design
2718 SW Kelly Street
Suite 181
Portland
Oregon 97201
USA
Tel. (503) 796 1368

Pro-Cite
Personal Bibliographic Software
Woodside
Hinksey Hill
Oxford OX1 5AU
UK
Tel. (0865) 730275
Fax (0865) 736354

Reference Manager:
SilverPlatter Information Ltd
10 Barley Mow Passage
Chiswick
London W4 4PH
UK
Tel. (0800) 282133
Fax (081) 995 5159

Association of Surgeons of Great Britain and Ireland

Br. J. Surg. 1992, Vol. 79, October, 1011-1013

A meeting of the Association of Surgeons of Great Britain and Ireland took place in Jersey on 1–3 April 1992. The President of the Association, Professor T. George Parks, was in the chair.

Iliofemoral *versus* femorofemoral bypass: a 6-year audit

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Iliofemoral and femorofemoral crossover bypass operations performed over a 6-year period were reviewed. A total of 226 patients underwent 231 operations from 1984 to 1990. Seventy-two patients had 75 iliofemoral grafts and 154 patients had 156 femorofemoral grafts. The early mortality rate was 6 per cent for the iliofemoral group and 1·3 per cent for femorofemoral reconstruction. There was a higher reoperation rate in the iliofemoral group (31 versus *16·0 per cent). The cumulative patency rate at 6 years was 75 per cent for iliofemoral bypass and 92 per cent for the femorofemoral procedure* ($P < 0{\cdot}01$)*, while the survival rates for the same period were 55 and 74 per cent respectively* ($P < 0{\cdot}01$)*. Hospital stay was significantly shorter for patients undergoing femorofemoral bypass* ($P < 0{\cdot}05$).

In unilateral iliac artery occlusive disease when endoluminal therapy is not possible the main reconstructive options are iliofemoral bypass or femorofemoral crossover bypass. Iliofemoral bypass is orthotopic and in the past was assumed to be superior to the femorofemoral procedure because of theoretical considerations with respect to blood flow[1]. However, it is a more extensive procedure which makes it a less attractive option for high-risk patients. Furthermore, subsequent disease progression proximal to the graft to involve the contralateral iliac artery has been reported[2,3]. Femorofemoral bypass was traditionally reserved for the high-risk patient unable to tolerate a major operation. It is a simpler procedure and high patency rates have been reported. The contralateral donor side should not be compromised and subsequent progression of atherosclerosis may even be retarded[4,5]. The success of femorofemoral bypass has prompted wider indications for its use and some authors now recommend this as the procedure of choice in unilateral iliac occlusive disease[6]. A possible drawback is that it involves operating on the contralateral asymptomatic groin, which carries some risk[3]. There is considerable variation in the reported success rates for both operations and controversy about which is preferable[7]. Both procedures are performed regularly in this department and the results of experience over a 6-year period are presented.

Patients and methods

Between 1984 and 1990, 231 operations were performed on 226 patients. Seventy-five iliofemoral bypass procedures were performed on 72 patients; the male female ratio was 58.14 with a mean age of 65 (range 39–87) years. A total of 156 femorofemoral bypass operations were performed on 154 patients, the male.female ratio was 125:29 and the mean age 67 (range 43–94) years.

Information on all vascular reconstructions performed from 1984 onwards is stored on a computer database and further data were obtained from the patients' medical records. Patients were called back for outpatient review in mid-1991. Non-attenders were followed up where possible by direct contact at home or via their general practitioners. Data were obtained on age, sex, indications for surgery, and preoperative risk factors. Cardiac risk factors were defined as a history of myocardial ischaemia, documented valvular disease, or medication for arrhythmia or cardiac failure. Cerebrovascular risk factors were defined as a history of stroke or transient ischaemic attack Hypertension was deemed a risk factor if a patient was receiving antihypertensive medication. Chronic obstructive airway disease and diabetes were other significant risk categories. Angiographic reports and operation records were reviewed to obtain details of angioplasties performed, types of graft used, and the sites of anastomoses

Postoperative complications, rates of reoperation and length of hospital stay for both procedures were compared. Life-table analysis was performed to assess cumulative survival and patency rates For cumulative patency, failures were defined as the first incidence of graft occlusion (i e. a primary patency rate was calculated). Patients who died or who were lost to follow-up were excluded from each interval. The generalized Wilcoxon test[8] was used to compare life-tables between the two groups. Hospital stay was compared by Wilcoxon rank analysis

Results

The operations performed each year are shown in *Figure 1* The number of femorofemoral bypass procedures showed a rising trend, whereas the number of iliofemoral bypasses performed

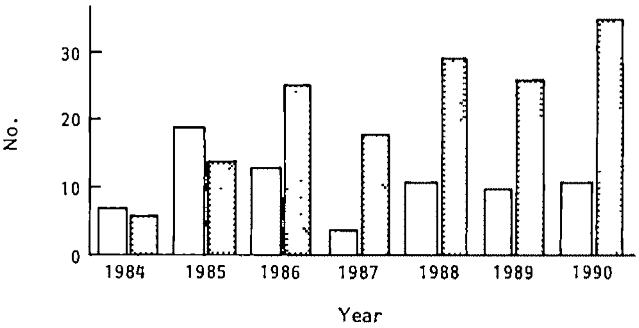

Figure 1 *Number of iliofemoral* (□) *and femorofemoral* (□) *bypass operations performed*

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remained relatively constant. In the latter years, femorofemoral procedures predominated markedly over the number of iliofemoral bypasses *Table 1* lists the indications for surgery, the most common of which were claudication and rest pain with or without tissue loss. Preoperative risk factors did not differ markedly between the two groups, as indicated in *Table 2*.

Selection of a patient for iliofemoral or femorofemoral bypass was based on consultant preference, the first choice procedure varying over the period studied This reflected the growing acceptance of, and the broadening indications for, femorofemoral bypass[6]. The grafts most commonly used were 8 and 10 mm Dacron (Du Pont, Stevenage, UK), in that order of frequency. Reversed vein grafts were infrequent (1 per cent in the iliofemoral group and 1·9 per cent in the femorofemoral group). The recipient arteries for the outflow end of these grafts are summarized in *Table 3*. Interestingly, the popliteal artery was used as recipient in one crossover bypass procedure. In the femorofemoral group, angiography showed a degree of stenosis in the donor side iliac system in 45·9 per cent of cases, but preoperative angioplasty was required in only 25·5 per cent

There were four early deaths (6 per cent) documented in the iliofemoral group: two from myocardial infarction, one from left ventricular failure and one from a cerebrovascular accident. In patients undergoing femorofemoral bypass, the two early deaths (1·3 per cent) were from myocardial infarction and a ruptured dissecting thoracoabdominal aneurysm. Early (<30 days) local postoperative complications are shown in *Figure 2*. The early reoperation rate was 11 per cent for iliofemoral bypass, for ischaemia (six), graft infection (one) and haemorrhage (one), and 5·1 per cent for the femorofemoral procedure, for ischaemia (four), haemorrhage (two), lymph leak (one) and compartment syndrome (one). *Table 4* lists the non-fatal general complications arising in the early period after operation. One patient undergoing femorofemoral bypass developed urinary retention and required subsequent transurethral resection of the prostate. The remaining complications

Table 1 *Indications for operation in iliofemoral and femorofemoral bypass*

	Iliofemoral bypass (*n* = 75)	Femorofemoral bypass (*n* = 156)
Disabling claudication	47	51·3
Rest pain/tissue loss	28	34·0
Graft occlusion	16	5·1
Acute ischaemia	1	4·5
Aneurysm	4	1·9
Trauma	3	1·9
Graft infection	1	0·6
Graft haemorrhage	0	0·6

Values are percentages. Occlusion of a previous graft was an indication in 16 per cent of iliofemoral bypasses, compared with only 5·1 per cent in femorofemoral bypass

Table 2 *Preoperative risk factors*

	Iliofemoral bypass (*n* = 75)	Femorofemoral bypass (*n* = 156)
Cardiac	68	69·3
Myocardial infarction	29	26·9
Angina	18	23·1
CABG	0	1·0
Heart failure	8	6·7
Atrial fibrillation	11	8·7
Valvular heart disease	3	2·9
Hypertension	34	35·6
Cerebrovascular	16	21·2
Stroke	11	15·4
Transient ischaemic attack	5	5·8
Diabetes	13	16·3
Respiratory	5	10·6
COAD	5	9·6
Bronchial carcinoma	0	1·0
Other	10	7·7
>1 of the above	13	14·4

Values are percentages. CABG, coronary artery bypass graft, COAD, chronic obstructive airway disease

Table 3 *Recipient arteries used in iliofemoral and femorofemoral bypass*

	Iliofemoral bypass (*n* = 75)	Femorofemoral bypass (*n* = 156)
Profunda femoris	51	30·8
Common femoral	47	65·4
Superficial femoral	1	3·2
Previous graft	1	0
Popliteal	0	0·6

Values are percentages

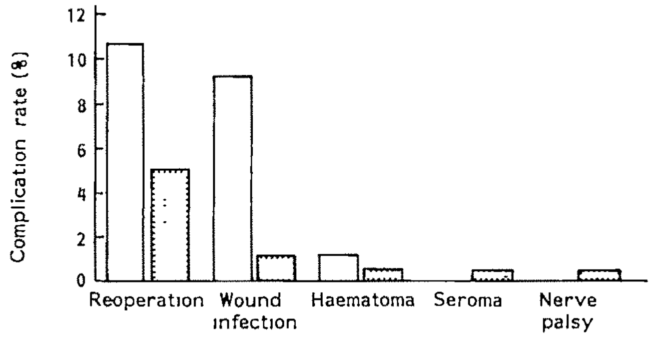
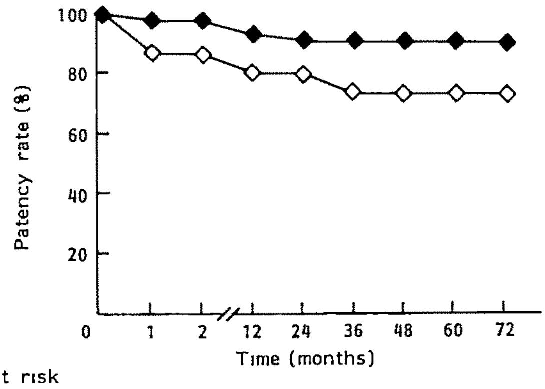


Figure 2 *Early (<30 days) local complication rate in iliofemoral (□) and femorofemoral (□) bypass*

Table 4 *Non-fatal early (<30 days) general complications in iliofemoral and femorofemoral bypass*

	Iliofemoral bypass (*n* = 75)	Femorofemoral bypass (*n* = 156)
Myocardial infarction	5	1·9
Chest infection	5	3·9
Ileus	3	0
Pseudomembranous colitis	1	0
Urinary retention	0	1·9
Renal dysfunction	0	1·3
Stroke	1	0
Deep vein thrombosis	1	0·6

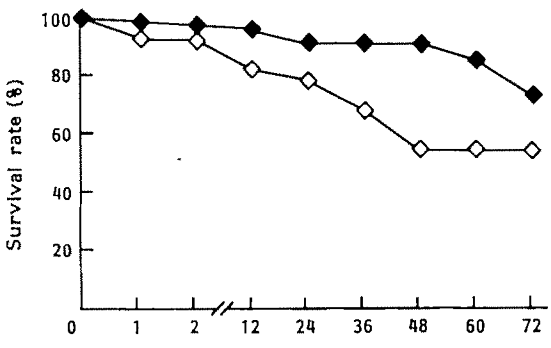
Values are percentages



Grafts at risk

	0	1	2	12	24	36	48	60	72
Iliofemoral	72	70	48	28	22	16	10	8	4
Femorofemoral	154	150	124	90	61	40	27	18	6

Figure 3 *Cumulative primary patency rate in iliofemoral (◇) and femorofemoral (◆) bypass* (P < 0·01, *generalized Wilcoxon test*)



Patients at risk

	0	1	2	12	24	36	48	60	72
Iliofemoral	72	71	53	35	28	22	18	14	10
Femorofemoral	154	152	127	92	70	47	34	23	14

Figure 4 *Cumulative survival rate in iliofemoral* (◇) *and femorofemoral* (◆) *bypass* ($P < 0\cdot01$, *generalized Wilcoxon test*)

were managed conservatively. Overall, 40 patients required 48 reoperations (early and late combined). In the iliofemoral group, 17 patients required 23 reoperations, giving a reoperation rate of 31 per cent, compared with 23 patients undergoing femorofemoral bypass who required 25 reoperations, giving a reoperation rate of 16·0 per cent. Reoperations on the contralateral side were not significantly more frequent in the iliofemoral group (8 *versus* 4·5 per cent for femorofemoral bypass), as has been reported by some authors[2,3]. The mean hospital stay was 10·7 (range 1–42) days for iliofemoral bypass and 8·6 (range 1–94) days for the femorofemoral operation ($P < 0\cdot05$). Cumulative rates of patency and survival for both groups are summarized in *Figures 3* and *4*. The femorofemoral procedure resulted in significantly higher patency and survival rates ($P < 0\cdot01$).

Discussion

The procedure of choice for unilateral iliac artery occlusive disease remains controversial and the value of retrospective studies has been questioned[7]. However, audit may be of benefit[9]. Femorofemoral bypass has gained popularity because of its simplicity and associated reports of long-term patency rates[6,10–12] of 80–86 per cent. Iliofemoral bypass is more orthotopic and may result in better haemodynamics[1]; with careful patient selection based on angiographic appearances, patency rates in excess of 90 per cent have been achieved[13,14]. However, poorer results have also been reported for both operations[2,14,15] and studies vary considerably in patient numbers, risk factors, indications, and length of follow-up, making direct comparisons impossible. Where statistical methods have been used retrospectively to generate comparable iliofemoral and femorofemoral groups, it has been found that there is no significant difference in patency rate[16].

In the present study, the two patient groups were broadly similar as regards age and sex distribution. However, a poorer outcome was seen for iliofemoral bypass. It is noteworthy that occlusion of a previous graft was a more frequent indication for surgery in the iliofemoral group and the greater use of the profunda femoris as recipient artery in iliofemoral bypass reflects a poorer quality of run-off. Some authors[17] have recommended adding a femoropopliteal graft in these cases to improve run-off and long-term patency. These factors may explain the lower patency and higher reoperation rates seen in the iliofemoral group. The lower survival rates in these patients may be a product of increased complication and reoperation rates, but may equally be due to patients being more susceptible to complications as a result of more advanced disease. General risk factors (*Table 2*), however, did not differ significantly between the two groups. Notably, the indications for femorofemoral bypass were wide, including low-risk patients.

An increasing preference for femorofemoral bypass is reflected in *Figure 1*, and a sizeable subset of patients in the femorofemoral group underwent preoperative iliac angioplasty of a stenotic lesion of the donor site. Significant (> 50 per cent) donor stenosis compromises long-term patency[5] and underlies the importance of preoperative biplanar angiography[12] Combining angioplasty with crossover bypass provides an option for patients with bilateral iliac disease who might otherwise require more extensive surgery. The utilization of this technique in low-risk patients probably explains the excellent long-term patency rate achieved in the femorofemoral group.

This was not a randomized controlled study, which is thought to be required by some[7]. Nevertheless, this audit suggests that femorofemoral bypass may be a more favourable option than iliofemoral bypass, with a significantly shorter hospital stay and lower complication and reoperation rates.

Acknowledgements

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Quality of life following surgery for abdominal aortic aneurysm

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Repair of abdominal aortic aneurysm (AAA) carries a considerable rate of morbidity and mortality, but little information exists on the quality of life following this procedure. During 1988 and 1989, in two hospitals, 211 patients (186 men and 25 women; median age 74 (range 48–87) years) underwent surgery for AAA. There were 77 ruptured aneurysms and 134 electively repaired. Of these, 38 patients died in hospital (27 ruptured, 11 elective); by the time of review a further eight (one ruptured, seven elective) had died from unrelated causes. Of the 165 survivors, 131 (45 ruptured, 86 elective) were reviewed and questioned as to their physical and mental state before and after surgery. Using the Rosser index, a value for quality of life before and after surgery was calculated (1·0, good; 0, dead). The value for the elective group was 0·94 before operation and 0·96 after, but in the ruptured group fell from 0·98 before surgery to 0·87 afterwards. This study shows that patients undergoing elective surgery for repair of AAA retain good quality of life. By contrast, patients surviving emergency surgery following this procedure seem to suffer a deterioration in life quality, which must be endured for the same expected lifetime as that for the elective group. These results support the need for a national AAA ultrasonographic screening programme.

Emergency surgery for ruptured abdominal aortic aneurysm (AAA) carries a considerable mortality rate, with values as high as 50 per cent[1–3]. The mortality rate associated with elective repair ranges from 1 to 10 per cent[4]. Little is known, however, of the quality of life of survivors following successful aortic surgery.

The aim of this study was to evaluate the change in quality of life experienced by patients surviving AAA repair. A comparison of health states before and after operation was made and the results for patients undergoing elective surgery compared with those treated for ruptured AAA.

Quality of life is a quantitative assessment of ability/disability and level of distress. Calculation of quality-adjusted life years (QALYs) is one of the popular methods used by managers and healthcare economists to measure the outcome of treatment[5]. One year of perfect health is defined as 1 QALY; a year of life at reduced quality q is q QALYs. The quality reduction factor q is calculated using a classification system such as that described by Rosser and Watts[6] (*Table 1*). This system was used to evaluate the quality of life of a cohort of patients who had undergone surgery for elective repair or for ruptured AAA

Patients and methods

In 1988 and 1989, 211 patients underwent repair of AAA at the Bristol Royal Infirmary and the Royal Devon and Exeter Hospital (*Table 2*) There were 186 men and 25 women of median age 74 (range 48–87) years An aneurysm was defined as ruptured if a rupture was found at operation; all other procedures were classed as elective repair The patients surviving from this period were invited to attend for interview at which they were questioned using the York quality of life questionnaire[7]. All information was obtained from the patients personally

Of 165 survivors, 131 (79 per cent) were interviewed The ruptured group contained 42 men and three women of median age 78 (range 62–87) years There were 78 men and eight women in the elective group of median age 71 (range 48–84) years. The median follow-up was 30 (range 18–42) months.

Patients were asked to answer a series of questions relating to their level of disability and distress at the time of interview and just before operation. Disability was assessed by ascertaining general mobility (from no difficulty to bedridden), self care (such as washing and dressing), and social and personal relationships (including social activities, hobbies and sex life). Each interview took approximately 30 min.

By scoring the completed questionnaires, each patient was allocated a health state consisting of a level of disability (I–VIII) and a level of distress (A–D)[6], as shown in *Table 1*. Using this system each health state is assigned a quality of life (QoL) rating, and a total value was calculated for each group. The matrix scoring system used to translate these data[7] is shown in *Table 3*. QoL is always <1, where 1 is perfect health and 0 is dead. Results have been expressed solely as collective

Table 1 *Rosser classification of illness states Each patient is allocated a disability score and a distress score*

Disability	
I	No disability
II	Slight social disability
III	Severe social disability and/or slight impairment of performance at work. Able to do all but very heavy housework
IV	Choice of work or performance at work very severely limited. Elderly people able to do light housework only, but able to go shopping
V	Unable to undertake any paid employment Unable to continue any education Elderly people confined to home except for escorted outings and short walks, and unable to do shopping
VI	Confined to chair or wheelchair or able to move around only with support from an assistant
VII	Confined to bed
VIII	Unconscious
Distress	
A	None
B	Mild
C	Moderate
D	Severe

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Table 2 *Number of deaths and survivors interviewed among patients undergoing abdominal aortic aneurysm repair*

	Elective	Ruptured	Total
Total no. of repairs	134	77	211
Deaths			
Hospital	11	27	38
Subsequent	7	1	8
Survivors at follow-up	116	49	165
Interviewed	86	45	131

Table 3 *Matrix used for calculation of quality of life values from Rosser health states*

Disability score	Distress score			
	A	B	C	D
I	1·000	0·995	0·990	0·967
II	0·990	0·986	0·973	0·932
III	0·980	0·972	0·956	0·912
IV	0·964	0·956	0·942	0·870
V	0·946	0·935	0·900	0·700
VI	0·875	0·845	0·680	0·000
VII	0·677	0·564	0·000	−1·480
VIII	−1·030	—	—	—

Table 4 *Quality of life values before and after operation*

	QoL value*	
	Before operation	After operation
All patients	0·95	0·93
Elective group	0·94	0·96
Ruptured group	0·98	0·87

*1·0, perfect health; 0, dead

QoL: QALYs have not been calculated. A value was calculated for three patient groups: all patients, elective patients; and those who had had ruptured aneurysms. QoL was calculated for states before and after operation.

Results

The collective QoL values are shown in *Table 4*. A difference was evident between the ruptured and elective groups: the elective group score rose from 0·94 to 0·96, but that of the ruptured group fell from 0·98 to 0·87.

In the ruptured group two patients had either moderate or severe distress ratings (Rosser state C or D) before operation; after surgery this number increased to seven. In contrast, before elective repair 16 patients were in moderate or severe distress and only eight remained in this category after surgery.

Men were questioned about sexual function. Of 119 with previously normal sexual function, 38 (32 per cent) complained of a decrease in potency, which manifested as inability to achieve erection in 82 per cent and failure to ejaculate in the remainder. There was no significant difference in loss of potency in the elective compared with the ruptured group. In this respect there was also no significant difference between those having a tube or a bifurcated graft or between results at the two hospitals.

Discussion

The means of calculating QoL and QALYs is fully explained by the Health Economics group at the University of York[5,7]. QoL data are collectively assessed for a group of patients and are not mean values in the statistical sense. This means that statistical analysis of the data must be viewed with caution, but results will suggest trends that can be identified. The fall in QoL in the ruptured group from 0·98 (near-perfect health) to 0·87 represents considerable disability: it is equivalent to a patient with slight social disability and mild distress becoming severely limited in performance at work with maximal distress. This is because the fall from 1·0 to 0 is logarithmic not linear, so a small numerical change is highly significant (*Figure 1*).

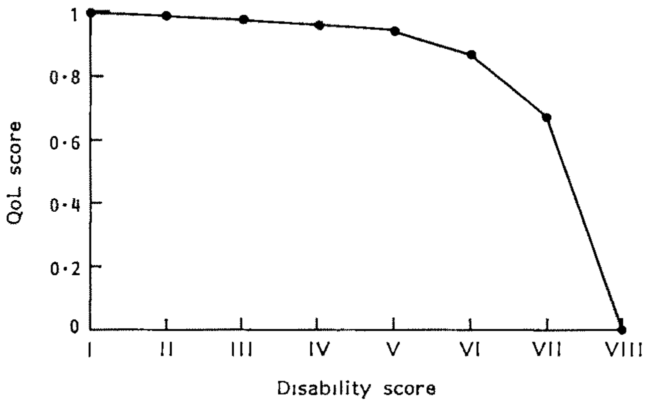

Figure 1 *Change in quality of life (QoL) score with increasing Rosser disability score in patients with no distress*

QALYs have not been calculated. To obtain QALYs, assumptions must be made about how QoL relates to time in a given group. Such assumptions must then be mathematically incorporated into the data[7]. This is one of the 'qualms about QALYs' that Smith wrote of in his article of the same name[8]. In addition, QALYs are usually employed to compare cost-efficiency of treatment, which was not under investigation in the present study[9–11]. QALYs for aortic surgery would be swayed towards elective repair because of the high mortality rate associated with surgery for ruptured aneurysm.

It has been reported by van Ramshorst *et al.* that patients surviving more than 30 days after repair of ruptured AAA have the same life expectancy as an age- and sex-matched population[12]. They also found no significant difference in life expectancy of survivors in a ruptured group compared with survivors in an elective group; this has been confirmed by Rohrer *et al.*[13]. Patients in the present series who have survived a ruptured aneurysm will, therefore, endure lower quality of life for the same life expectancy as the elective group.

Quality of life after AAA surgery has also been investigated by these authors[12,13]; van Ramshorst *et al.* investigated it using a different system from that used in the present study, but showed no significant difference between elective and ruptured groups[12], contrary to the present findings. Rohrer *et al.* found that general well-being was significantly higher in the elective group[13].

The method of data collection in these two studies was different from that employed in the present study. The use of self-completion questionnaires or telephone interviews as a means of collecting data, common in assessment of life quality, was avoided in the present study as it was felt that a meeting with the patient would yield more complete and reliable information; emphasis was also placed on obtaining information from the patient rather than from relatives or general practitioners. Direct questioning revealed a surprisingly high rate of sexual dysfunction in men. This complication was recognized in 1969 and reports of its frequency vary from 0 to 80 per cent for aortoiliac surgery[14–16]. Injury to the hypogastric plexus combined with altered pelvic haemodynamics is often the cause[16].

The mortality rate associated with ruptured AAA and the diminished quality of life endured by survivors augments the argument for screening for this condition[17–19].

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Synchronous aortic and gastrointestinal surgery

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The synchronous performance of aortic and gastrointestinal surgery may hold an increased risk of aortic graft infection. The experience of one surgeon who performed 32 such synchronous operations over a period of 11 years is reviewed. No graft infection occurred and it is concluded that such combined operations may be safer to perform than staged surgery in elderly patients.

It is generally held that the synchronous performance of aortic graft and gastrointestinal tract surgery should be avoided because of the risk of subsequent graft infection. Some authors suggest caution is needed if a concomitant procedure is contemplated, and that the gastrointestinal operation can usually be deferred[1]. However, the risk of graft infection following synchronous surgery varies in different reports[2] and some feel that cholecystectomy combined with aortic graft surgery may be preferable to the possibility of postoperative acute cholecystitis[3].

There are some patients in whom concomitant disease of the gastrointestinal tract is discovered at the time of aortic surgery; this includes benign or malignant gastric or duodenal ulcers, cholecystitis or common bile duct (CBD) stones, diverticulitis and colonic carcinoma. There are two possible approaches: one procedure (usually the vascular) is carried out at that time and the second operation deferred to a later date, or both procedures are performed under the same anaesthetic. The former approach requires two major operations within the space of a few weeks, whereas the latter requires only one general anaesthetic but with a theoretically increased risk of aortic graft infection.

This paper reviews a series of patients under the care of one surgeon (J.F.K.) who have been managed with synchronous aortic graft and gastrointestinal surgery. Patients who needed gastrointestinal surgery for a life-threatening condition have been excluded and only those for whom synchronous surgery was indicated, but not imperative, are discussed.

Patients and methods

Between 1980 and 1991, 32 patients underwent synchronous aortic graft and gastrointestinal surgery There were 23 men and nine women with a median age of 70 (range 55–86) years. During the study period three patients underwent emergency colectomy for an ischaemic or perforated colon along with aortic surgery. These were life-threatening conditions for which treatment could not have been delayed; they have been excluded from this study.

Of the 32 patients, 20 had biliary surgery. All those who underwent cholecystectomy had a severely diseased gallbladder, evidence of acute cholecystitis, an obstructed gallbladder or had suffered recurrent episodes of biliary pain before their aneurysm operation. Two of these patients also underwent exploration of the CBD for stone removal None of these patients had simple asymptomatic gallstones. Nine patients had gastric surgery· seven truncal vagotomy and pyloroplasty for benign peptic ulcer disease, one total gastrectomy for an operable carcinoma, and one excision of a gastric ulcer. The final three patients underwent bowel surgery: right hemicolectomy for a bleeding diverticulum, anterior resection for carcinoma, and small bowel resection for jejunal diverticulitis.

Results

There was only one postoperative death, which occurred in a 78-year-old man who had an aortic graft for aneurysm and truncal vagotomy and pyloroplasty for a scarred duodenum with active ulceration. Following surgery, urine output was poor and renal failure and a necrotic buttock developed. The patient died 6 days after surgery from renal failure due to trash embolization into the renal arteries.

Four patients required a second laparotomy. This second procedure was respectively for ischaemic ileum, intra-abdominal bleeding, oversewing of an acute gastric erosion, and drainage of a subphrenic abscess following cholecystectomy. Two patients developed wound infection and two had pyrexia for which no cause was found (one had a haematoma drained); a further patient had a pneumonia. Limb ischaemia required lower-limb amputation (below- and through-knee respectively) in two patients.

No patient developed evidence of any form of graft sepsis in the immediate postoperative period and none has subsequently developed evidence of graft infection. Long-term follow-up revealed two patients who required further surgery. In one an operation was performed for retained stones in the CBD 9 years after the original surgery; this patient required a further operation for incisional hernia 6 months later. In the second patient a suprarenal aortic aneurysm developed and ruptured 7 years after the first procedure. A further two patients developed an incisional hernia.

Discussion

There are a number of patients with large ($>5{\cdot}5$ cm) aortic aneurysms who also have serious gastrointestinal pathology It is often policy to treat these by staged operations because of the theoretical risk of infecting a vascular prosthesis by synchronous surgery. However, the gastrointestinal pathology or its serious nature may be discovered only at laparotomy. A decision must then be made whether to deal with the two conditions synchronously or to stage the procedures, dealing with the greater perceived threat first.

Although two general surgical procedures may be carried out synchronously, surgeons are cautious about performing gastrointestinal tract surgery at the same time as introducing a foreign body into the abdomen, especially a vascular graft[1]. The main reason for this is the increased chance of graft infection with its risk of serious sequelae. However, there are also risks involved with leaving a surgically correctable condition, especially the danger of postoperative cholecystitis[4–6] or haemorrhage from a peptic ulcer, and synchronous surgery should at least be considered. Occasionally, as in the patients discussed with jejunal diverticulitis or acute gallbladder pain, abdominal pain in the presence of a large aneurysm is misdiagnosed as an aortic rupture.

In the present series there was a high morbidity rate, as reported elsewhere[1], but only one death. All the patients who underwent further surgery while in hospital (laparotomy in three, laparotomy with amputation in one, amputation alone in one) survived to be discharged. There was no indication that the performance of two procedures simultaneously significantly increased the risks over those of a single procedure, although in a series from the Mayo Clinic[7] there was an unexpected increase in morbidity attached to two operations. The majority of the synchronous procedures involved operations on the

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biliary tract. In several series of combined biliary and aortic surgery[6–8] there were no deaths attributed to cholecystectomy, although there was one graft infection. It is unlikely that recent developments in biliary surgery, such as laparoscopic cholecystectomy and endoscopic retrograde cholangiopancreatography, will make much difference to the management of patients with acute gastrointestinal and aortic pathologies, although where staged procedures are acceptable they may reduce the severity of one of them.

In conclusion, this small series has not shown any increased risk of graft infection after synchronous aortic and gastrointestinal surgery. Synchronous operations should be given consideration when faced with dual bowel and vascular pathology in the abdomen.

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Vein compliance: a preoperative indicator of vein morphology and of veins at risk of vascular graft stenosis

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Compliance measurements of 53 long saphenous veins before femorodistal bypass have been performed using a duplex scanner with venous occlusion for distension. These have been compared with the histological features of the veins. There was significantly more moderate or severe focal hyperplasia and circular muscle hypertrophy in distal long saphenous vein than in its proximal counterpart ($P < 0{\cdot}01$ *and* $P < 0{\cdot}05$ *respectively). The mean (95 per cent confidence interval) compliance of distal vein with moderate or severe hyperplasia was 0·16 (0·13–0·19) compared with 0·29 (0·22–0·36) for that with no, minimal or mild hyperplasia* ($P = 0{\cdot}001$)*. The mean compliance of distal vein with moderate or severe muscle hypertrophy was 0·19 (0·17–0·21) and of vein with no, minimal or mild hypertrophy 0·25 (0·21–0·29)* ($P = 0{\cdot}14$)*. The mean lowest compliance in seven patients who developed stenosis was 0·10 (0·07–0·13) compared with 0·21 (0·16–0·26) in the rest* ($P < 0{\cdot}001$)*. Preoperative measurement of vein compliance can be used to identify vein with marked pre-existing intimal hyperplasia and as a predictor of future graft stenosis.*

Femorodistal bypass has become an important treatment option for limb salvage. Autogenous vein is still regarded as the best conduit for reconstruction whether used *in situ*, reversed, or as part of a composite graft[1–3]. The 5-year failure rate for femorodistal bypass[3] ranges from 20 to 75 per cent and suggests that even vein is not without its problems.

Poor-quality vein is associated with lower patency rates[4,5]. Graft failure that occurs between 1 month and 1 year after implantation is generally the result of graft-related stenosis Such stenosis is caused by intimal hyperplasia; vein graft failure secondary to hyperplasia is now well documented[6–11]. Intimal hyperplasia in animal experiments has been shown to correlate well with loss of compliance of the venous conduit after implantation into the arterial circulation[12].

Despite the use of vein grafts for over half a century, only recently have the changes of intimal fibrosis and sclerosis in vein been documented before cardiac[13–15] and femoropopliteal bypass[16 17] surgery. Previous qualitative studies have shown that intimal hyperplasia and other changes are present in vein before its insertion as an arterial conduit. This study was conducted to determine whether similar changes are seen at the proximal and distal ends of the long saphenous vein (LSV), and if these changes can be identified by measuring preoperative venous compliance. The compliance results were then compared with the development of graft stenosis.

Patients and methods

A group of 53 patients who had their LSV mapped before femorodistal bypass and whose graft was patent at 30 days were included in the study Vein compliance was measured using a technique of venous occlusion that has previously been validated[18], and which is summarized below. With the patient at 15° of reversed Trendelenberg tilt, preoperative diameter measurements of the LSV were performed using an ATL Ultramark 9 duplex scanner (Advanced Technology Laboratories, Stevenage, UK) with a 10-MHz sector scanner head Diameter measurements (D) were performed at the groin, mid-thigh, knee and mid-calf Measurements at mid-thigh, knee and mid-calf were also performed with venous occlusion using a sphygmomanometer cuff inflated until venous flow was seen to stop by using B-mode and Doppler ultrasonography. The pressure (p) required to occlude venous flow was noted The change in diameter (d) was recorded. The assumption was made that, as the resting venous pressure in the LSV[19] is <5 mmHg, p represents the change in pressure. Compliance (C) was calculated using the equation[20]:

$$C = \frac{d}{D\,p}$$

In the validation study the mean (95 per cent confidence interval) vein compliance ratio measured in 35 normal LSVs was 0·26 (0·22–0 30) using this technique; the intraobserver coefficient of variation for the method[18] ranged between 2 06 and 3 41

At the time of surgery vein samples were taken from the proximal and distal ends of vein and stored in 10 per cent formal saline Using light microscopy with haematoxylin and eosin, and van Gieson staining, semiquantitative grading (minimal, I, mild, II; moderate, III, severe, IV) as described by Milroy *et al*[17] was used to quantify the degree of intimal hyperplasia (focal or eccentric) and muscle hypertrophy (circular and longitudinal) The specimens were examined 'blindly' by one of the authors (E.S.) on two separate occasions with agreement in the scoring of 94 per cent of the specimens. The histology of the distal vein specimen was compared with the nearest compliance measurement

Follow-up was performed at 6 weeks, and 3, 6, 9 and 12 months using colour duplex ultrasonography and intra-arterial digital subtraction angiography to diagnose graft stenosis.

Numbers are expressed as mean (95 per cent confidence interval) Statistical analysis was performed using the Mann–Whitney U test, analysis of variance (ANOVA) and χ^2 test with Yates' correction.

Results

The mean compliance of the vein was 0·25 (0·21–0·29) at the mid-thigh, 0·27 (0·20–0·34) at the knee and 0·26 (0·22–0 30) at the calf; there was no statistically significant difference between the groups (ANOVA). The number of LSVs showing both types of hyperplasia and muscle hypertrophy in the proximal and distal vein is shown in *Table 1*. There were significantly more distal veins showing changes of focal

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hyperplasia (grades III and IV) and circular muscle hypertrophy ($P < 0{\cdot}01$ and $P < 0{\cdot}05$ respectively) than their proximal counterparts. *Table 2* shows the distribution of the internal vein diameter at the groin, mid-thigh, knee and mid-calf in the 53 patients

The mean lowest compliance of distal vein with evidence of grade III or IV hyperplasia (focal and diffuse) was 0·16 (0·13–0·19) compared with 0·29 (0·22–0·36) in those with no or grade I or II hyperplasia ($P = 0{\cdot}001$). The lowest mean compliance of distal vein with evidence of grade III or IV muscle hypertrophy (circular and longitudinal) was 0·19 (0·17–0·21) and in vein with evidence of no or grade I or II hypertrophy 0·25 (0·21–0·29) ($P = 0{\cdot}14$).

The mean follow-up was 9·4 (minimum 6) months. The mean lowest compliance value in the seven patients who developed stenosis was 0·10 (0·07–0·13) compared with 0·21 (0·16–0·26) in the rest ($P < 0{\cdot}001$) (*Figure 1*). All seven had evidence of grade III or IV intimal hyperplasia (focal or diffuse) and four had grade III or IV muscle hypertrophy (longitudinal or circular) in the distal vein specimen. There was no significant difference in the mean time of follow-up between the group of patients with and that without stenosis. The mean time at which the stenoses occurred was 5·4 months; one was detected at the 6-week follow-up. During this period one graft, which had been identified as having a stenosis, occluded and was satisfactorily revised. All the other grafts with stenosis underwent an interventional procedure. *Table 2* also indicates that actual vein diameter is not a good predictor of graft stenosis, as stenoses are seen to occur in the larger veins.

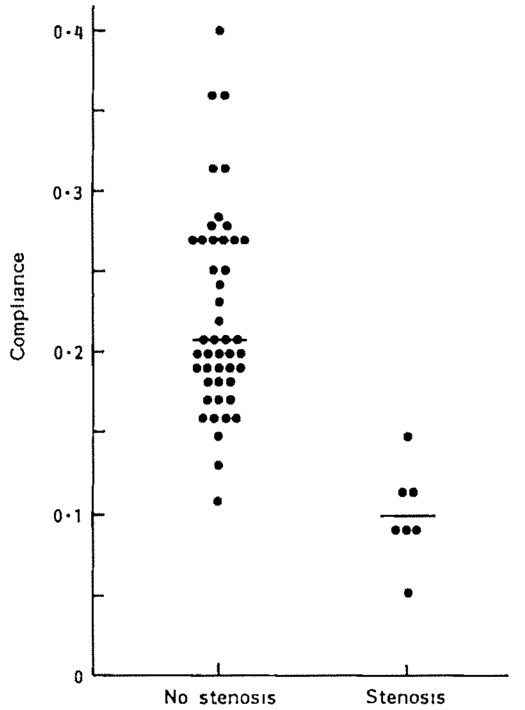

Figure 1 *Relationship between graft compliance and the development of graft stenosis* (n = 53, P = 0·001, *Mann–Whitney* U *test*) *Bars are means*

Table 1 *Number and distribution of histological abnormalities found in the long saphenous vein*

	Grade							
	Proximal				Distal			
Histology	I	II	III	IV	I	II	III	IV
Intimal hyperplasia								
Focal	6	4	0	2	4	5	8	4
Diffuse	3	4	10	4	3	3	8	8
Muscle hypertrophy								
Circular	0	6	7	2	4	9	11	3
Longitudinal	2	6	6	6	5	5	7	6

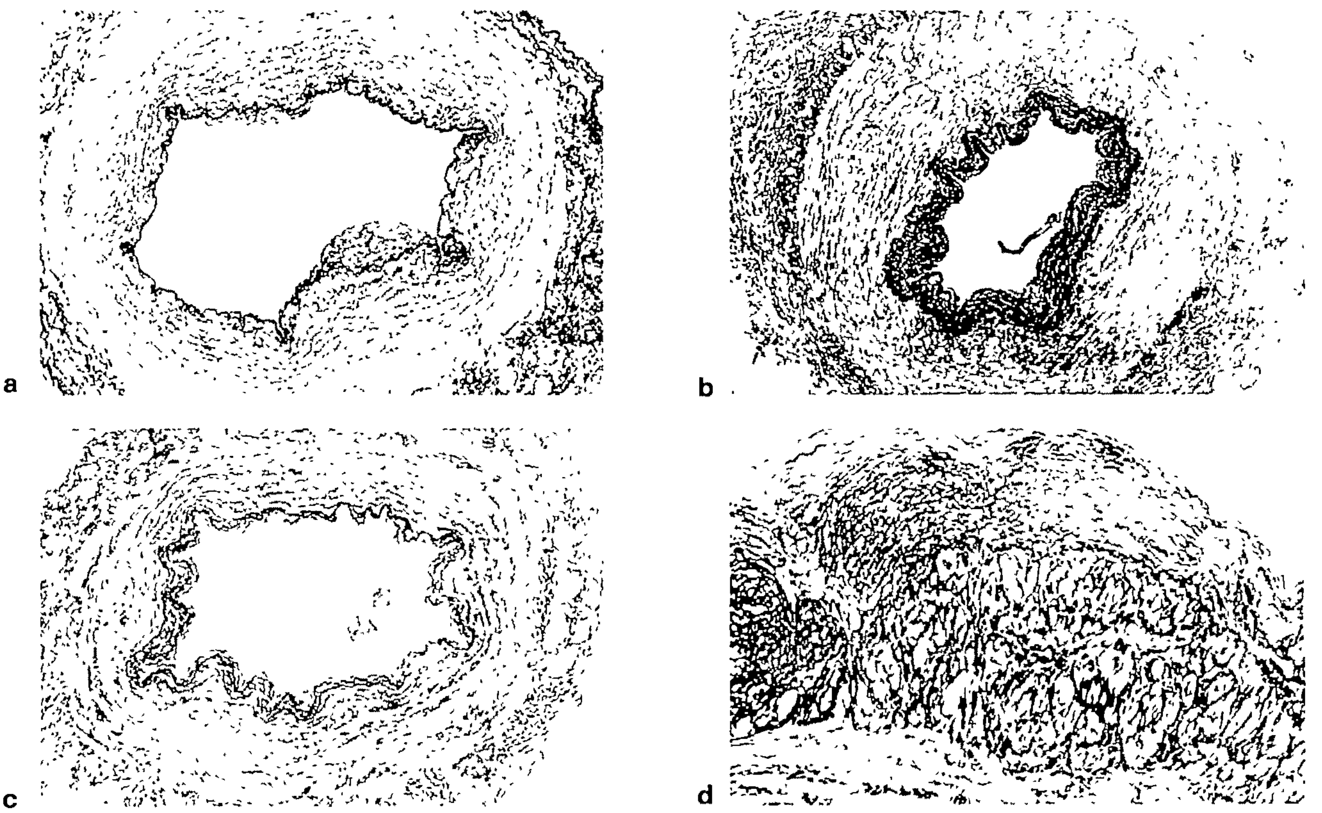

Figure 2 **a** *Focal hyperplasia;* **b** *diffuse hyperplasia,* **c** *circular muscle hypertrophy,* **d** *longitudinal muscle hypertrophy* (*Van Gieson stain, original magnification for* **a**–**c** ×40 *and for* **d** ×150)

Table 2 *Distribution of internal vein diameter and numbers within each group that developed stenosis*

	≤3mm	>3–5 mm	>5 mm
Groin	4 (2)	35 (4)	14 (1)
Mid-thigh	14 (2)	31 (4)	8 (1)
Knee	16 (3)	32 (3)	5 (1)
Mid-calf	32 (3)	20 (4)	1 (0)

Values in parentheses are numbers of stenoses

Figure 2 shows histological examples of focal and diffuse intimal hyperplasia, and of circular and longitudinal muscle hypertrophy.

Discussion

An increasing number of femorodistal reconstructions are being performed[3] and there is proven benefit in terms of patency from graft surveillance[21,22]. It has been suggested that vein with changes of intimal hyperplasia may be more likely to undergo graft stenosis[16] and so it would be useful to be able to identify such vein before operation. This would allow the selection of an alternative conduit or the introduction of an intense graft surveillance programme.

The process of intimal hyperplasia has been shown in animal experiments to alter the compliance of the implanted conduit[12]. It has also been documented that 'stiff' grafts have a poorer patency than compliant ones[23]. The results of this study confirm those of other investigators that marked 'abnormal' changes may be seen in the histological appearance of vein before bypass. This study has further shown that such changes may occur in both the proximal and distal vein.

Previous workers have suggested that the development of intimal hyperplasia in vein and prosthetic grafts is associated with altered haemodynamics[24–26], changes in circumferential wall tension[27,28], wall stress[29–31], surgical trauma, and mural ischaemia[26,27,32]. Abbott and Megerman in 1989 suggested that there is a 'missing link' in the cause and effect of intimal hyperplasia[33]. In view of the present findings it may be that the above factors act as promoters or potentiators of an already ongoing disease process rather than being initiators of intimal hyperplasia.

Compliance measurement can detect the vein with high-grade intimal hyperplasia. Compliance is not affected to such an extent by muscle hypertrophy. Since all the veins that developed a graft stenosis had grade III or IV intimal hyperplasia, the ability to identify this feature before operation seems important. Furthermore, four of these affected grafts had grade III or IV muscle hypertrophy and the combination of these features was probably responsible for the poor compliance found in the veins used.

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Risk of rupture of postangiographic femoral false aneurysm

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The surgical management of 50 false aneurysms caused by transfemoral arterial catheterization was reviewed to document the incidence and effects of rupture before repair. Twelve false aneurysms ruptured, leading to shock in six patients, distal ischaemia in three and stroke in one. The mean(s.d.) time from catheterization to rupture was 2·8(1·7) (range 1–6) days. Postoperative complications occurred in seven patients with ruptured and eight with non-ruptured aneurysms ($P < 0{\cdot}04$)*. The mean(s.d.) age of patients with ruptured aneurysms was 67·2(6·3) (95 per cent confidence interval 63·5–70·8) years and those without 58·5(9·1) (95 per cent confidence interval 55·3–61·7) years* ($P < 0{\cdot}008$)*. On multiple regression analysis, age, peripheral vascular disease and raised plasma liver enzyme levels on admission were found to be significant independent predictive variables for rupture (all* $P < 0{\cdot}05$*). It is recommended that patients with these risk factors undergo urgent operative correction of femoral false aneurysm.*

Percutaneous transfemoral arterial catheterization is the most commonly used method for coronary and peripheral arteriography and is associated with fewer puncture-site complications than is the brachial route[1]. False aneurysm developing in the groin after arterial catheterization (*Figure 1*) can cause significant morbidity and usually requires surgical repair. Such iatrogenic injury occurs infrequently but the incidence has risen in proportion to the increased demand for arterial catheterization[2]. As with aneurysm formation elsewhere, rupture may occur but, as most published series are small, not enough is known about the incidence and effects of this complication. This study attempts to elucidate the clinical course of these lesions, to evaluate factors that may be associated with increased morbidity, and to identify patients who require urgent intervention.

Patients and methods

The review encompassed all patients who were operated on in this hospital for false aneurysm resulting from transfemoral arterial catheterization. The study was limited to the 10-year period starting 1 January 1980 Patients were identified by examination of the theatre records of the vascular surgery unit and were included only if the operative findings confirmed the presence of a false aneurysm Data were gathered on a standard pro forma by retrospective review of case notes, 100 per cent retrieval was achieved.

Anticoagulation with heparin was discontinued at least 12 h before catheterization in all cases and no patient receiving warfarin therapy who had a prothrombin time > 1 7 times the control value underwent the procedure All cardiac catheterizations during the course of the study were performed using 8-Fr catheters with haemostatic sheaths; 5000 units heparin was usually given intravenously at the start of the procedure and its effect reversed with protamine sulphate on completion. Radiological procedures were carried out using 5-Fr catheters without sheaths The same dose of heparin was given, but only to patients undergoing renal or subclavian artery angioplasty In all cases manual compression was maintained for 10 min after removal of the catheter or sheath, in the absence of subsequent bleeding a pressure dressing was applied and the patient kept on bed rest If bleeding persisted beyond 10 min, manual compression was continued until bleeding ceased, after which the pressure dressing was applied. On return to the ward the dressing was checked, the distal circulation assessed, and vital signs observed every 15 min for 2 h and thereafter at 4-h intervals All wounds were inspected the morning after the procedure and if satisfactory the patient was mobilized

After a review of the medical and nursing progress notes the clinical course of each patient was assigned to one of three groups. There were 20 stable, 18 enlarging and 12 ruptured false aneurysms at the time of surgery. They occurred in 35 women and 15 men with a mean(s d.) age of 61(9 2) years

Analysis was carried out using Complete Statistical System software (StatSoft, Tulsa, Oklahoma, USA) on a Compaq 386s/20 (Compaq, Richmond, Surrey, UK) computer. The χ^2 test with Yates' correction, where appropriate, was used for discrete variables and the Mann–Whitney U test for continuous variables. Statistical significance was accepted at $P < 0\ 05$

Results

Incidence

A total of 47 false aneurysms complicated 11 122 cardiac procedures (0 42 per cent) and three followed 3396 radiological procedures (0·09 per cent) ($\chi^2 = 9{\cdot}62$, 1 d.f, $P < 0{\cdot}002$). Nine of the cardiac and all three of the radiological false aneurysms ruptured ($\chi^2 = 6\ 16$, 1 d.f , $P < 0{\cdot}02$).

Clinical features

Of the 12 false aneurysms that ruptured, eight did so while the patient was walking and in one while straining at stool. Two patients had been discharged from hospital when rupture occurred The mean(s.d.) time from catheterization to rupture was 2·8(1·7) (range 1–6) days. In only two cases did rupture occur while the patient was under observation with the diagnosis of a false aneurysm already made.

Systemic hypotension followed rupture in six patients, in one of whom a profound left-sided weakness developed. This recovered after repair and the patient subsequently underwent right carotid endarterectomy. Seven patients required blood transfusion of up to 10 units each. In three patients distal ischaemia complicated rupture; this was remedied by resuscitation and emergency repair of the aneurysm in two. However, in one patient ischaemia persisted after repair and, at a second operation, an intimal dissection of the external iliac artery was revealed. Intimal suture with vein-patch angioplasty was sufficient to restore the distal circulation. None of the non-ruptured false aneurysms was associated with shock or distal ischaemia.

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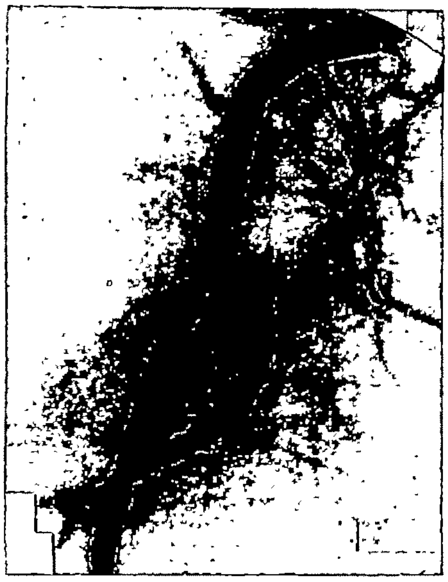

Figure 1 *Digital subtraction arteriography showing false aneurysm of the superficial femoral artery following transfemoral arterial catheterization*

Table 1 *Complications after surgical repair of false aneurysm*

Complication	Non-ruptured aneurysm ($n = 38$)	Ruptured aneurysm ($n = 12$)
Wound infection	4 (11)	5 (42)*
Femoral neuralgia	4 (11)	1 (8)
Haematoma (drained)	1 (3)	3 (25)
Myocardial infarction	0 (0)	1 (8)
Stroke	0 (0)	1 (8)
Death	1 (3)	0 (0)

Values in parentheses are percentages. Stable and enlarging false aneurysms were combined as non-ruptured because of the small number of individual complications *$\chi^2 = 4{\cdot}07$, 1 d.f., $P < 0{\cdot}04$

Complications after operative repair

Complications developed after the repair of four stable (20 per cent), four enlarging (22 per cent) and seven ruptured (58 per cent) false aneurysms ($\chi^2 = 6{\cdot}06$, 2 d.f., $P < 0{\cdot}05$). Complications are shown in *Table 1*. All four patients with haematomas requiring drainage and five of those without developed wound infections ($\chi^2 = 14{\cdot}23$, 1 d.f., $P < 0{\cdot}001$). Details of patients with wound infections are given in *Table 2*. A drain was inserted before closure of the wound in 20 patients; five of these wounds became infected compared with four without drains ($\chi^2 = 1{\cdot}11$, 1 d.f., $P < 0{\cdot}30$). Five patients with ruptured (42 per cent) and two with non-ruptured (5 per cent) false aneurysms required further surgery ($\chi^2 = 7{\cdot}24$, 1 d.f., $P < 0{\cdot}007$).

Factors predisposing to rupture

Patient details were reviewed in a search for factors that might have predisposed to rupture. Factors found not to have a significant association included blood pressure (systolic, diastolic and mean) either during catheterization or over the next 48 h, and antiplatelet and thrombolytic therapy. No association was found with heparin or warfarin therapy given after catheterization. Mobilization on the first day after the procedure as opposed to continued bed rest was not associated with an increased incidence of rupture.

The mean(s.d.) age of patients with ruptured aneurysms was 67·2(6·3) (95 per cent confidence interval 63·5–70·8) years and of those without 58·5(9·1) (95 per cent confidence interval 55·3–61·7) years ($z = -2{\cdot}67$, $P < 0{\cdot}008$). Factors found to be significantly more common in patients with rupture are shown in *Table 3*. Anticoagulation with heparin was present before catheterization in three patients with ruptured (25 per cent) and in one with non-ruptured (3 per cent) false aneurysm ($\chi^2 = 3{\cdot}53$, 1 d.f., $P < 0{\cdot}06$).

Table 2 *Details of nine patients who developed wound infections*

Patient no	Reoperation	Prophylactic antibiotics	Culture result	Time to wound healing (days)
1	Haematoma drainage	Yes	*Enterococcus* Coliforms	46
2	Haematoma drainage	Yes	Coliforms	50
3	Endarterectomy	Yes	*Bacteroides* *Enterococcus*	21
4	None	Yes	Coliforms	43
5	Haematoma drainage Debridement (twice)	Yes	Coliforms *Bacteroides*	55
6	None	No	Coliforms	46
7	Haematoma drainage Delayed primary suture	Yes	Coliforms	87
8	None	No	*Staphylococcus aureus* Coliforms	17
9	Abscess drainage Delayed primary suture	Yes	*Bacteroides* Coliforms	40

Table 3 *Factors predisposing to false aneurysm rupture*

Factor	Non-ruptured aneurysm ($n = 38$)	Ruptured aneurysm ($n = 12$)	χ^2	P
Peripheral vascular disease*	3 (8)	5 (42)	5·43	0·005
Raised liver enzyme levels*	2 (5)	5 (42)	7·24	0·001
Precatheterization warfarin	5 (13)	5 (42)	4·63	0·031
Age ≥65 years*	9 (24)	9 (75)	6·48	0·011

Values in parentheses are percentages 1 d f *Significant at $P < 0{\cdot}05$ on multiple regression analysis

Discussion

Because of the infrequent occurrence of symptomatic false aneurysm after transfemoral catheterization, all of the major published series are retrospective. As the present series is one of the largest it is reasonable to draw some inferences from the data.

The rate of formation of false aneurysm that required surgical repair after cardiac catheterization (0·42 per cent) is consistent with those quoted in similar studies (0·2–0·42 per cent)[2,3]. The rate of occurrence after radiological procedures (0·09 per cent) is also comparable to the value of 0·1 per cent quoted in the largest published series[2].

The rate of false aneurysm formation requiring surgery was significantly higher after cardiac catheterization than after radiological procedures. Possible reasons for this include the larger catheter size and the use of a haemostatic sheath, both of which have been reported to increase the rate of false aneurysm formation[2]. Patients with aortic valvular incompetence have been shown to be at higher risk of developing arterial injuries after percutaneous arterial catheterization[4], and it is likely that there would be a greater proportion of these patients in the cardiac catheterization group.

A recent report of 150 vascular complications after cardiac catheterizations included two fatalities after false aneurysm rupture[5]. In the present study of 50 false aneurysms treated surgically, 12 ruptured, leading to shock in six patients – obviously a potentially life-threatening state in patients who have concomitant heart and cerebrovascular disease Acute ischaemia of the affected limb complicated rupture in three patients. This may have been caused by systemic hypotension with underlying arterial occlusive disease or by extrinsic pressure on the femoral artery from the sudden expansion of the haematoma. In one patient arterial dissection caused by the catheter was at least partly responsible. In all cases appropriate surgery restored the distal circulation and there was no resultant tissue loss.

Surgical treatment of vascular complications of cardiac catheterization is followed by a reported postoperative complication rate[3,6] of 20–28 per cent. The complication rate after surgery of 30 per cent in this study confirms the significant morbidity that accompanies the surgical correction of these iatrogenic lesions There were significantly more complications after surgery for rupture than when the aneurysm was dealt with while stable or enlarging (58 *versus* 20 and 22 per cent respectively) ($P < 0{\cdot}05$). This increased morbidity rate may be accounted for by hypotension resulting from the sudden reduction of the circulating blood volume, the local effect of haemorrhage into the tissues of the thigh, and the greater age and therefore higher susceptibility to concomitant disease in this group. The reoperation rate was also significantly higher after rupture

Wound infection was a significant problem associated with delayed wound healing, despite prophylactic antibiotics being given in most cases The infection rate of 11 per cent for non-ruptured aneurysms is higher than might have been expected in clean surgical cases and it is believed that prior catheterization at the same site is likely to have precontaminated the operative field. The infection rate of 42 per cent after rupture was significantly higher ($P < 0{\cdot}04$) and is testimony to the disruption caused. All the patients who developed postoperative haematomas requiring drainage went on to become infected, confirming established surgical principles.

The overall rate of femoral neuralgia of 10 per cent is considerably lower than that of 50 per cent reported by Hallett *et al.*[7]. It was interesting that the incidence of femoral neuralgia in ruptured cases was similar to that in non-ruptured, despite the large haematomas formed in the thigh and the increased number of reoperations. This may imply that this complication results from trauma inflicted by the catheter itself rather than from the false aneurysm or surgical repair. However, in a retrospective study such as this, the true rate may be underestimated.

Patients whose aneurysms ruptured were significantly older. Multiple regression analysis showed that peripheral vascular disease was a significant independent predictive variable for rupture. It could be argued that a higher peripheral resistance in patients with arterial occlusive disease might have accentuated the pressure within the lumen of the false aneurysm Anticoagulation treatment before catheterization was more common in the ruptured aneurysm group. However, commencement or continuation of such therapy after catheterization was not associated with an increased incidence of rupture. This may be because a false aneurysm is initially a haematoma in communication with the arterial lumen. Hence it would be susceptible to the continuing effects of precatheterization anticoagulation therapy, which may increase the likelihood of rupture. Once the aneurysm had become more established and strengthened by peripheral organization and fibrosis it would be less likely to rupture. In the patients in this series this process may have taken up to 6 days as no false aneurysm ruptured beyond this time, when 33 were still present. An association was also seen with raised liver enzyme concentrations in the blood. This was usually a non-specific elevation due to hepatic congestion from right-sided heart failure and may have caused an increase in the prothrombin time leading to an anticoagulant effect at the time of catheterization No increase in the incidence of rupture was found with mobilization on the first day after the procedure compared with continued bed rest. However, of the 12 aneurysms that ruptured, eight did so while the patient was walking and one while straining at stool. It has been speculated that patients receiving antiplatelet therapy would be at risk of rupture of false aneurysms[3] but this was not the case in this series.

Cardiac catheterization with 8-Fr catheters caused 47 of the aneurysms and radiological procedures with 5-Fr catheters caused three. Although it is likely that, once formed, the false aneurysms from the different procedures would behave in a similar fashion, the patients in the two groups would have different characteristics. It was found that patients undergoing radiological procedures for peripheral vascular disease were less likely than those having cardiac catheterization to develop a symptomatic false aneurysm; once formed, the aneurysms in the former group were more likely to rupture This may be because of the older age and higher prevalence of peripheral vascular disease in these patients, both of which were significant independent risk factors for rupture.

Colour-flow Doppler ultrasonography and duplex scanning have recently been shown to have high sensitivity and specificity for detection of false aneurysm after arterial catheterization[8,9]. Using these methods a significant number of unsuspected false aneurysms have been detected in patients with bruising after catheterization, the majority of which have been observed to thrombose spontaneously on serial scans[10,11]. Ultrasonographically guided compression has been advocated as a first line of treatment for these lesions, with success claimed in 27 of 39 cases[12]. On the basis of these reports, policies of initial conservative management are being advocated, with surgery reserved for those aneurysms that either enlarge or do not settle[5,10,11]. In the present series only two false aneurysms had been correctly diagnosed before rupture Therefore, to prevent rupture with compression therapy, all patients would have to be screened after transfemoral arterial catheterization.

We recommend that patients suspected of having a false femoral aneurysm should be put on strict bed rest. Urgent repair in those aged over 65 years is advocated, and in those with peripheral vascular disease, raised plasma liver enzyme concentrations or anticoagulant therapy just before catheterization. Such patients are prone to rupture, with its attendant morbidity, and repair after rupture is associated with significantly more complications.

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Reperfusion injury in skeletal muscle: a prospective study in patients with acute limb ischaemia and claudicants treated by revascularization

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A study was carried out to document the occurrence of rhabdomyolysis and renal complications in patients undergoing vascular reconstruction. Indices of muscle damage and renal function were monitored before, during and for up to 10 days after vascular reconstruction for a variety of conditions ranging from intermittent claudication to acute ischaemia. Seven patients with acute limb ischaemia (group 1) and nine with intermittent claudication (group 2) were studied prospectively. In group 1, median creatine kinase (CK) and myoglobin levels were markedly raised 24–48 h after surgery (CK, 29 370 units/l; myoglobin, 8·17 mg/l). Myoglobin reached its peak concentration and declined more quickly than CK, but both indices gave similar information about the extent of muscle damage. In contrast, patients undergoing elective surgery for claudication showed no significant departure from reference values for myoglobin or CK. All patients in group 1 underwent fasciotomy to relieve raised compartmental pressures and five were treated with alkali and mannitol to produce diuresis. Despite these measures, two patients suffered renal failure (peak creatinine levels 611 and 590 μmol/l) after successful revascularization and subsequently required haemodialysis; these patients did not have diuresis. One of these patients died following a stroke 8 days after surgery; the other survived and was discharged with a normal limb and restored renal function. There was no evidence of muscle damage or renal complications in group 2. It is concluded that: (1) the risk of muscle damage and renal complications is minimal in patients undergoing elective surgery for intermittent claudication; (2) in patients who present acutely, revascularization after several hours of ischaemia leads to rhabdomyolysis and high levels of circulating CK and myoglobin (despite fasciotomy there was evidence of subsequent muscle damage); (3) it is not possible to predict which patients will go into renal failure; and (4) in all acutely ischaemic patients there is a risk of renal complications and it is suggested that prophylactic measures, such as an alkaline diuresis and mannitol infusion, be instituted during or before the operation as a matter of course.

Haimovici[1] was the first to draw attention to the complication of acute renal failure after successful revascularization of the ischaemic limb. Sporadic reports of muscle necrosis, sometimes accompanied by renal damage, have followed and there has been a good deal of experimental work, mainly in animals, investigating this topic[2]. It is now recognized that reperfusion injury is the same phenomenon as the crush injury first described by Bywaters and Beall[3] in 1941. The detailed mechanism of injury is unclear and the nature of the initial insult and the time course of the damage for human muscle remain to be elucidated[4].

Salvage of limbs rendered acutely ischaemic by arterial thrombotic and embolic disease or trauma is commonly undertaken; successful limb salvage is sometimes followed by renal failure. If not adequately treated by dialysis this can have lethal consequences. This report is a prospective study of a number of cases of acutely ischaemic limbs before, during and after successful revascularization. Levels of plasma creatine kinase (CK), serum myoglobin and plasma creatinine were recorded. Another group of patients undergoing elective bypass for intermittent claudication was similarly studied and their results compared with those from the group with ischaemia. Muscle biopsies for histochemical analysis were obtained from three patients in the latter group. The renal failure that occurred in two patients with ischaemia is described and some suggestions made about prophylaxis against renal failure.

Patients and methods

Seven consecutive patients (four men and three women, age range 40–89 years) admitted as emergencies suffering from acute limb ischaemia (group 1) were studied with nine others (five men and four women, age range 26–72 years) admitted for bypass surgery for intermittent claudication alone (group 2) Patients 1, 2, 5 and 6 in group 1 suffered massive ischaemia of the whole limb to the groin or shoulder, indicated by pallor, coldness, and motor and sensory loss. Patient 4 suffered ischaemia to groin level to a moderate degree in that motor function was intact. Patients 3 and 7 had severe ischaemia up

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Table 1 *Group 1 clinical details, treatment and outcome in seven patients admitted as emergencies with acute limb ischaemia*

Patient no	Age (years)	Sex	Presentation	Time to operation (h)	Anatomy	Procedure	Outcome
1	59	M	Massive left lower limb ischaemia	24	Left iliac artery thrombosis	Femorofemoral crossover bypass with fasciotomy	Renal failure Dialysis Recovery from renal failure and limb salvage
2	41	M	Patchy ischaemic right lower limb (intra-arterial drug injection 'trash limb')	12	Injection into right femoral artery Good distal pulses	Fasciotomy Alkaline diuresis Mannitol	Deep vein thrombosis Limb salvage
3	61	F	Pregangrenous left lower limb	24	Left superficial femoral artery block	Femoropopliteal vein bypass and fasciotomy Alkaline diuresis Mannitol	Salvage of knee Below-knee amputation Normal renal function
4	69	M	Moderate right lower limb ischaemia (rest pain)	24	Right iliac artery thrombosis	Aortofemoral bypass and fasciotomy Alkaline diuresis Mannitol	Limb salvage Normal renal function
5	89	M	Massive left upper limb ischaemia	6	Left axillary artery occlusion from dislocated left shoulder and brachial plexus injury	Subclavian–brachial artery bypass Fasciotomy, alkaline diuresis and mannitol	Limb salvage with brachial plexus
6	75	F	Massive left lower limb ischaemia	8	Unilateral left iliac artery occlusion from embolus	Embolectomy Fasciotomy	Renal failure Stroke Amputation Death
7	40	F	Pregangrenous right lower limb	24	Right limb aortofemoral bypass occlusion	Femorofemoral crossover bypass and fasciotomy Alkaline diuresis Mannitol	Salvage of right lower limb Normal renal function

Table 2 *Group 2. clinical details, treatment and outcome in nine patients with claudication admitted for elective reconstructive surgery*

Patient no	Age (years)	Sex	Presentation	Anatomy	Procedure	Outcome
8	70	F	Left calf claudication	Left superficial femoral artery block	Left femoropopliteal bypass	Patent bypass
9	61	F	Right calf claudication	Right superficial femoral artery block	Right femoropopliteal bypass	Patent bypass
10	62	F	Left calf claudication	Left superficial femoral artery block	Left femoropopliteal bypass	Patent graft
11	71	F	Left calf claudication	Left superficial femoral artery block	Left femoropopliteal bypass	Patent graft
12	53	M	Right thigh claudication	Right iliac artery occlusion	Femorofemoral crossover bypass	Patent graft
13	70	M	Left calf claudication	Left superficial block	Left femoropopliteal bypass	Patent graft
14	26	M	Left calf claudication	Left calf iliac block	Left iliofemoral bypass	Patent graft
15	72	M	Left calf claudication	Occluded left femoropopliteal bypass	Repeat bypass using PTFE	Patent bypass
16	71	M	Right calf claudication	Occluded right iliac artery	Femorofemoral crossover bypass	Patent bypass

PTFE, polytetrafluoroethylene

to the upper thigh. The severity of ischaemia in all cases required surgery within 24 h. Patient 2, an intravenous drug abuser, underwent fasciotomy alone for an acute 'trash limb'-like condition[5] following self-injection of a gel form of temazepam[6]. The rest of group 1 underwent direct arterial surgery (*Table 1*). Patients in group 2 all underwent elective surgery for intermittent claudication alone with no ischaemia at rest (*Table 2*) The ankle-brachial pressure index was $>0\cdot7$ at rest and fell to $<0\cdot5$ after walking at 2 m.p.h ($3\cdot22 \times 10^3$ m/h) on a level treadmill for 5 min.

Preoperative, intraoperative and several postoperative blood samples were taken for estimation of myoglobin, CK, creatinine and electrolytes. Intraoperative samples were taken from the main vein draining the limb (i.e. the common femoral or axillary vein) before clamping the artery for reconstruction purposes and at 5 and 30 min after the release of clamps following reconstruction. Blood pH and gas analyses were performed in all cases before clamping and 5 min after clamp release. Compartmental pressures were measured in all patients in group 1 using a pressure monitor (Stryker Surgical, Puerto Rico, USA). In patient 5, after reconstruction, the axillary artery was flushed with warmed Hartmann's solution and the effluent collected via a cannula in the axillary vein. The effluent was analysed for potassium, myoglobin and CK. Muscle biopsies for histochemical analysis were taken from the anterior tibial compartment at intervals after reconstruction in patients 1, 2 and 5. Plasma creatinine and urine volumes were measured daily for up to 10 days after the operation.

Results

Index case

Patient 1 was a 59-year-old man admitted with massive left lower limb ischaemia as a result of a left iliac artery thrombosis. A femorofemoral crossover bypass was undertaken and the limb was successfully revascularized. After 24 h it was noticed that compartment pressures were rising and a three-compartment fasciotomy was performed. Despite this intervention and the administration of fluids, the patient became anuric with a plasma creatinine level of 230 μmol/l and a plasma CK concentration of 45 750 units/l. He underwent regular dialysis over the next 2 weeks and made a complete recovery; he now uses the limb normally.

As a result of this case it was decided:

1. To afford protection to the kidneys by instituting diuresis (200 ml urine/h, $\mathrm{pH} > 5$) with $1\cdot24$ per cent sodium bicarbonate infusion, together with mannitol ($0\cdot5$ g/kg) administered before release of clamps and repeated as necessary. The only exception was patient 6, who was already suffering from pulmonary oedema and in whom it was judged unwise to administer a further fluid or sodium load. This patient did not receive the bicarbonate and mannitol.

2. To undertake open fasciotomy at the time of reconstructive surgery or, if intracompartmental pressures are within 40 mmHg of the diastolic blood pressure[7], up to 48 h from the time of revascularization.
3. To investigate the time course of muscle damage to determine whether flushing the ischaemic limb before reconnecting it to the circulation would prevent soluble proteins from the damaged muscle reaching the kidneys.

Subsequent observations

In group 1, all limbs were saved following reconstructive surgery but additional distal amputation was required in patients 3 and 6. Had revascularization been ineffective, both patients would have required disarticulation at the hip. All patients in group 2 had successful reconstructive procedures and the ankle arterial blood pressures after operation rose significantly at rest and after treadmill exercise There was no evidence that the reperfusion muscle damage had any long-term consequences. Follow-up showed that, amputations permitting, normal use of the limb was restored.

In patient 5 the effluent from the axillary vein had a markedly raised potassium concentration of 7·1 mmol/l (Hartmann's fluid contains 5 mmol/l potassium). Specimens collected 5 and 30 min later, after circulation was restored, showed concentrations of >6·0 mmol/l (not due to haemolysis). The effluent also showed a raised concentration of CK (1400 units/l), but there was no additional increase in levels of this enzyme in blood samples from the axillary vein 5 or 30 min after release of clamps when the circulation was restored. The plasma CK level had risen to 27 000 units/l 48 h later. These results suggested that, although the raised potassium concentration was evidence of disturbed muscle metabolism, there was little evidence that release of muscle protein occurred during the period of ischaemia and rapidly entered into the circulation when the limb was revascularized. A relatively slow release of muscle proteins was also seen in other patients in group 1.

The myoglobin and CK levels in both groups are shown in *Table 3*. In group 1, levels before operation were generally normal (with the exception of patient 5 mentioned above). After release of clamps, there was no significant increase in concentration in the venous blood draining from the limb, and no difference between the 5- and 30-min samples The most pronounced increases were seen 24–48 h after operation ($P < 0{\cdot}05$ for both, Wilcoxon signed rank test). Thereafter levels fell to normal by day 3 for myoglobin and by day 10 for CK It is notable that myoglobin and CK levels both rose, but the former peaked earlier and cleared more quickly than CK in all cases. There was a significant correlation between the two peak levels with respect to baseline values ($r_S = 0{\cdot}94$, $P < 0{\cdot}04$). The contrast in the times of peak CK and myoglobin concentrations in patient 6 is shown in *Figure 1*. This pattern was typical of cases in group 1, although there were wide variations in the peak levels of myoglobin and CK (*Table 3*).

In group 2 there was little alteration in circulating CK or myoglobin concentrations from initially normal levels during or after reconstructive surgery. Although there was a modest rise in CK on days 1 and 2 ($P < 0{\cdot}02$), followed by a fall on

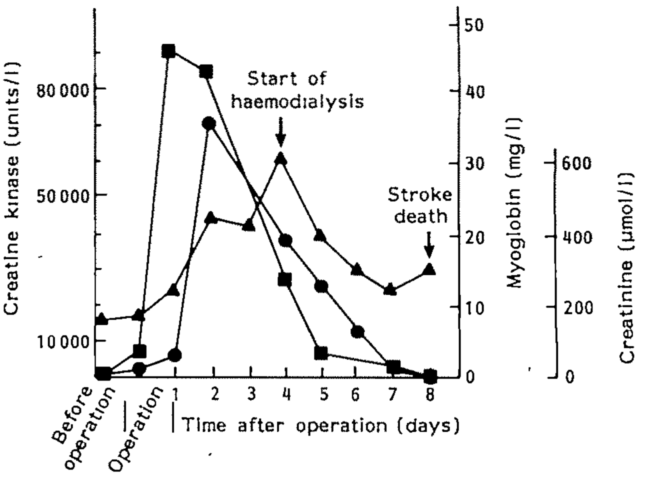

Figure 1 *Myoglobin (■), creatine kinase (CK, ●) and creatinine (▲) levels before, during and after operation in patient 6 This patient died from a stroke 8 days after operation, but the pattern of CK and myoglobin rise and fall was typical of group 1 patients*

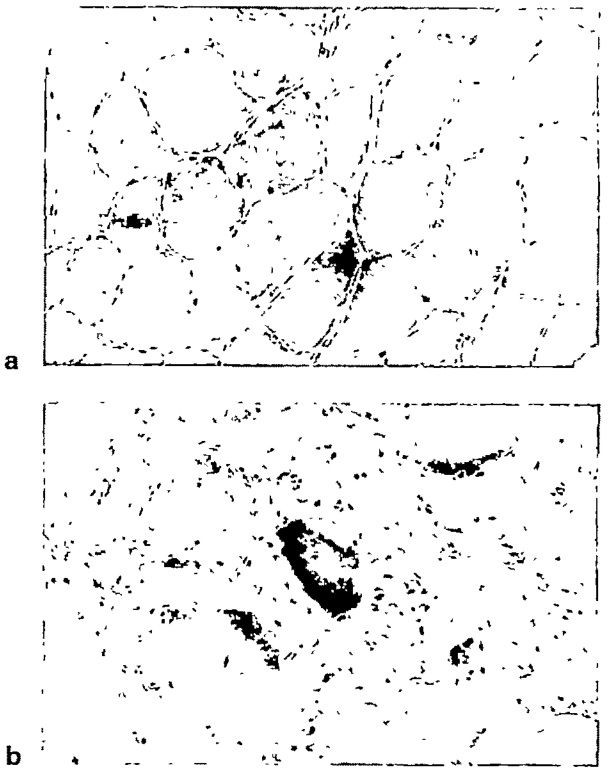

Figure 2 *Microscopy of muscle biopsy in patient 5 taken* **a** *at fasciotomy (note the relatively normal architecture) and* **b** *10 days after operation (note the disruption of muscle fibre and mononuclear cell infiltration). (Original magnification ×200)*

Table 3 *Myoglobin and creatine kinase levels before, during and after operation*

	Myoglobin (mg/l)*				Creatine kinase (units/l)†			
	Group 1	*P*§	Group 2	*P*§	Group 1	*P*§	Group 2	*P*§
Before operation	0·27 (0·08–2·02)		0·05 (0·05–0·10)		367 (38–1149)		64 (37–120)	
During operation‡	0·77 (0·06–12·6)	n.s	0·09 (0·05–0·73)	n.s	861 (65–1480)	n.s	76 (43–243)	n.s
After operation								
Days 1 and 2	8·17 (1·09–47·2)	<0·05	0·10 (0·06–0·31)	n.s	29 370 (1982–72 400)	<0·04	182 (78–753)	<0·02
Days 3–5	0·73 (0·15–14·3)	<0·04	0·06 (0·05–0·11)	n.s	8 720 (344–35 400)	<0·03	114 (30–160)	<0·01
Days 7–10	0·31 (0·05–2·38)	n.s	0·05 (0·05–0·09)	n.s	1 611 (148–3199)	<0·02	34 (26–104)	<0·05

Values are median (range) Normal values: * <0·09 mg/l, † <200 units/l. ‡Mean of venous samples 5 and 30 min after release of clamps §Wilcoxon signed rank test *versus* before operation; n.s., not significant days 3–5 and 7–10, the median values remained within the reference range (30–200 units/l) (*Table 3*).

Blood gas levels and pH were unremarkable in preclamp and postclamp specimens. In patient 5, one muscle specimen was obtained from the biceps during fasciotomy and another 10 days later. The earlier biopsy (*Figure 2a*) showed a relatively normal appearance with intact muscle fibres. The specimen at 10 days (*Figure 2b*) showed necrotic fibres, with mononuclear cell infiltration of the tissue and some signs of regeneration. The biopsies taken from the anterior tibialis during fasciotomy and 10 days later from patients 1 and 2 showed similar findings.

Patients 1 and 6 became anuric 48 h after operation when plasma creatinine levels were 611 and 590 μmol/l respectively. Both patients underwent successful haemodialysis, but patient 6 subsequently developed dense hemiplegia and died on day 8 after operation. In the other patients, one preoperative creatinine level was slightly raised (149 μmol/l), but all other measurements were within the normal reference range (80–120 μmol/l). The plasma creatinine level remained normal in group 2 with the exception of one patient in whom it peaked at 141 μmol/l 48 h after operation and stabilized at 128 μmol/l by the time of discharge.

Discussion

This study shows evidence of muscle damage with serum myoglobin and plasma CK concentrations as high as 350 times normal after successful revascularization in patients suffering from massive limb ischaemia. Such changes did not occur when revascularization was carried out in patients complaining only of effort ischaemia without rest pain. The results suggest that a high degree of ischaemia is necessary for muscle damage, and we assume that there is also a critical duration. It is generally thought that for skeletal muscle up to 60 min of ischaemia is tolerable without appreciable risk. Patients in group 1 had all had limb ischaemia for $\geqslant 6$ h when they came to surgery.

The mechanism of muscle damage is unclear, but there is current speculation about the role of free radicals in reperfusion damage to other tissues and in studies of ischaemic skeletal muscle in animals[8,9]. Free radicals may result from the action of activated neutrophils[10], xanthine oxidase[11], tumour necrosis factor[12] or by other means[4]. Release of oxygen free radicals by the action of such agents at the time of reperfusion has been implicated in muscle cell damage and subsequent rhabdomyolysis[12]. This hypothesis has led to the suggestion that oxygen free radical scavengers, such as superoxide dismutase, mannitol and catalase, and the xanthine oxidase inhibitor allopurinol, may be useful for prophylaxis[2].

Biopsy showed that histologically discernible muscle damage does not occur during the period of ischaemia but develops at some stage after revascularization. This observation is consistent with the measurements of plasma CK levels, although the data to determine whether the time course of CK release and the onset of histochemical damage are the same are not available. There was no evidence that reperfusion muscle damage had any long-term consequences; at follow-up use of the limb, so far as amputation permitted, appeared normal.

Renal failure is one of the consequences of rhabdomyolysis and in two patients in group 1 renal involvement required dialysis. These patients had high concentrations of circulating CK and myoglobin, but it is notable that other patients had similar levels but did not suffer any renal problem These two patients did not receive mannitol and diuretics, but with such small numbers it is not possible to draw firm conclusions about the role of alkaline diuresis and mannitol in the prevention of renal failure. Preoperative renal insufficiency would be a predisposing factor, but none of the patients studied had a raised plasma creatinine concentration before surgery except for patient 5, in whom levels fell to normal after reconstruction. Other causes of renal failure such as hypovolaemia, renal artery occlusion, mismatched blood transfusion, prolonged hypertension, drugs and massive sepsis must also be considered. None of these factors was present in any patient as indicated by clinical observations of body temperature, pulse and blood pressure. Our experience is that, in patients with acute ischaemia undergoing reconstructive procedures, myoglobinuria and possible renal failure should be anticipated and prophylactic precautions taken. Such measures include both fasciotomy and biochemical intervention.

Following reperfusion, damage to capillaries results in oedema in a compartment with unyielding osseofascial walls, giving rise to increased pressure, which leads to damage of muscle fibres and nerves. Relief of excessive pressure can be achieved by compartmental fasciotomy[13]. Intramuscular compartmental pressures are easily measured and are a useful guide. We perform fasciotomy after arterial reconstruction in any patient who has had motor or sensory dysfunction before surgery and/or when intracompartmental pressure rises to within 40 mmHg of diastolic pressure[7]. Although fasciotomy is accepted as a prophylactic procedure, the return of compartmental function is variable, and this measure is no guarantee against rhabdomyolysis and renal failure.

Biochemical measures may be considered at two levels. First, because myoglobin will precipitate in concentrated acid urine, an alkaline diuresis using sodium bicarbonate alone or with a loop diuretic should be induced[8]. An osmotic diuretic such as mannitol may also be useful[13]. Second, mannitol administration may help to neutralize destructive free radical species

We believe that prophylaxis against renal failure using fasciotomy and alkaline and osmotic diuresis is important when there has been successful revascularization of massive acute limb ischaemia. There may be a role for oxygen free radical scavengers[14] and allopurinol but, given the present state of knowledge, such drugs should ideally be used before the release of clamps and proper regard paid to their toxicity

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Colour-coded duplex ultrasonography in the selection of patients for endovascular surgery

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Endovascular surgery using angioplasty or atherectomy may potentially relieve the symptoms of claudicants with minimal morbidity, but results are best when short stenoses are treated. In this study, colour-coded duplex ultrasonography has been compared with angiography. In aortoiliac segments duplex examination had a sensitivity of 88 per cent and a specificity of 100 per cent; in femoropopliteal disease the sensitivity was 100 per cent and duplex scanning identified more disease than angiography. Subsequently, 73 symptomatic limbs with femoropopliteal disease were scanned to assess their suitability for endovascular surgery. Of these limbs, 27 (37 per cent) had suitable lesions and the remaining 46 (63 per cent) were spared angiography. Colour-coded duplex ultrasonography can reliably be used to select patients for endovascular surgery.

Patients with moderate intermittent claudication have traditionally been treated conservatively but the advent of percutaneous transluminal angioplasty and mechanical atherectomy offers the possibility of intervention with minimal morbidity. To exploit the potential benefits of these techniques there is a need to be able to select patients non-invasively before proceeding to hospital admission and arteriography. This study assessed the accuracy of colour-coded duplex ultrasonography in examining both the aortoiliac and femoropopliteal segments and the ability of this technique to identify lesions suitable for endovascular surgery.

Patients and methods

Three separate groups of patients were studied. In the first group, ten consecutive patients with peripheral vascular disease admitted for arteriography had their aortoiliac segments mapped using colour-coded duplex ultrasonography (Acuson 128; Acuson, Mountain View, California, USA). Scans were performed by one experienced examiner and included colour profile and spectral information on the distal aorta and the iliac arteries. Segments were identified by B-mode imaging and categorized as. (1) normal; (2) haemodynamically insignificant (<50 per cent stenosis), (3) haemodynamically significant (50–99 per cent stenosis); or (4) occluded.

Criteria for 50–99 per cent stenosis were a clear visualization of change in vessel diameter on B-mode ultrasonography or a doubling of the peak systolic velocity within the stenosis on Doppler scanning An artery was classified as occluded based on the absence of flow on Doppler examination During subsequent angiography, intra-arterial pressures were recorded from the distal aorta and iliac and common femoral arteries. Stenoses seen on arteriography were measured by senior radiologists who were unaware of the duplex scan results Percentage stenosis was calculated as the narrowest luminal diameter compared with normal artery next to the stenosis.

In a second group of 12 patients with intermittent claudication, 19 femoropopliteal segments were assessed by duplex scanning and results compared with those from arteriography. Arteries were insonated from the common femoral bifurcation to the mid-popliteal fossa by an experienced vascular technician. Each femoropopliteal artery was divided into three equal segments (proximal, middle and distal) and the same diagnostic criteria were used for analysis

A third group of patients had the femoropopliteal vessels examined by duplex scanning alone to assess their suitability for endovascular procedures. A total of 73 femoropopliteal vessels in 73 patients were scanned using colour-coded duplex ultrasonography. Using the same criteria, lesion length and percentage stenosis were calculated Isolated stenoses, occlusions <10 cm long, and multiple stenoses <10 cm in total length were considered to be suitable for either angioplasty or atherectomy

Results

Aortoiliac vessels

Duplex examination provided diagnostic information in 18 of 20 segments. Examination was difficult in one patient as he was obese and could not lie flat because of severe chronic pulmonary disease. Angiography identified seven stenotic lesions and one occluded segment. Duplex scanning correctly identified all normal aortoiliac segments, the occluded segment and six of the seven stenotic lesions; one segment that was normal on duplex examination had 50 per cent stenosis at the origin of the left common iliac artery. There was a significant (>20 mmHg) pressure drop across all stenoses >50 per cent, except one. There was no pressure difference even after intra-arterial papaverine in this stenotic iliac segment. Duplex ultrasonography had a sensitivity of 88 per cent and a specificity of 100 per cent when compared with angiography

Femoropopliteal vessels

Duplex scanning identified all normal and abnormal segments correctly and there was no significant difference in the length and percentage of stenosis as identified by duplex scan and angiography. There were 11 abnormal proximal segments and 14 abnormalities in both middle and distal segments. Two further lesions were identified by duplex scanning that were not visualized on angiography. One lesion was at the origin of the superficial femoral artery and the other at the level of the adductor canal. The overall sensitivity of duplex ultrasonography was 100 per cent, the specificity was, however, reduced as this method identified more disease than angiography (*Figure 1*).

Suitability for endovascular surgery

Of the 73 femoropopliteal vessels scanned, 27 (20 stenoses and seven occlusions) had lesions considered suitable for endovascular procedures. Fourteen patients had a single stenosis and six had an occlusion of <10 cm. The remaining seven patients had multiple lesions (six stenoses and one occlusion) but the total length of the stenoses or occlusion was <10 cm.

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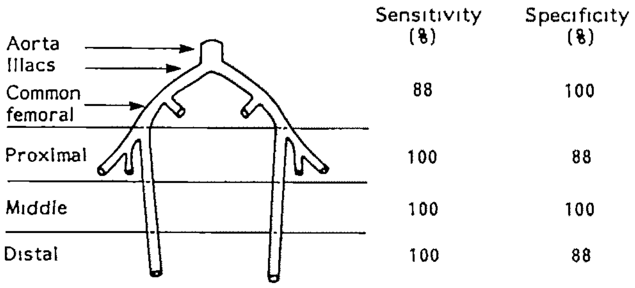

Figure 1 *Sensitivity and specificity of duplex ultrasonography compared with conventional angiography in aortoiliac and femoropopliteal segments*

Discussion

Balloon angioplasty, laser angioplasty and mechanical atherectomy devices have expanded the therapeutic options available for patients with moderate intermittent claudication who desire symptomatic relief without major surgery. The suitability of a particular patient for these procedures depends primarily on the location and extent of the lesion and it is therefore desirable to have a non-invasive method to show the extent of disease. Endovascular techniques are particularly suited to both the aortoiliac and femoropopliteal segments, and this study confirmed the findings of others[1] that duplex scanning is able to assess these vessels accurately. There are certain technical difficulties related to obesity, bowel gas and excessive abdominal movement, but these can usually be overcome with experience. Interpretation of biplanar angiograms specifically at the origin of the superficial femoral artery and at the adductor canal where the artery overlaps the femur can be difficult. It would seem that duplex ultrasonography may be more sensitive than conventional angiography in these areas. It is concluded that patients can be selected for minimally invasive techniques based on the findings of colour-coded duplex ultrasonography and that angiography is not required in making this decision.

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Prevalence of lower limb ulceration in an urban health district

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Before establishing a community leg ulcer programme, a survey was performed to assess the incidence and prevalence of lower limb ulceration in the Newcastle Health District. The prevalence was 1·9 per 1000 in patients over the age of 45 years, and the annual incidence 3·5 per 1000 in the same age group. Recurrent ulcers represented 47 per cent of the total and 50 per cent of all ulcers had been present for >6 months. District nurses spent 190 h per week in the community dressing leg ulcers, making a total number of 25 922 visits each year. In the treatment of leg ulcers 35 different types of dressing were used and only 14 per cent of ulcerated limbs were treated by appropriate compression. Of all patients with leg ulcers, 35 per cent had been seen by a hospital specialist but only 7 per cent had been examined by a vascular surgeon at any time.

Venous disease of the lower limb is a major problem in the community, causing suffering, a high cost to the National Health Service and loss of productivity[1]. Venous reflux, outflow obstruction and inefficient function of the calf muscle pump may lead to ulceration of the lower limb. Such ulceration has been reported to account for approximately 85 per cent of all leg ulcers[2], although this is difficult to assess as the diagnosis is imprecise and multiple aetiologies may be present. Leg ulcers of all aetiologies affect an estimated 400 000 people in the UK, with approximately 25 per cent being open and requiring treatment at any one time[3]. The overall prevalence of lower limb ulceration has been estimated by Cornwall *et al.*[4] to be 0·18 per cent with a female·male ratio of 2:1, by Dale *et al.*[5] to be 0 15 per cent and by Hansson *et al*[6] to be 0·2–0·4 per cent, although none of these studies involved investigations to exclude completely other causes of ulceration.

In the UK up to £600 million is spent annually in the treatment of ulcers of the lower limb; in Sweden the total cost of leg ulcer treatment has been calculated to be £26·8 million in a population of approximately 8 million, including the cost from loss of productivity[1]. Specialist leg ulcer clinics have been established in an attempt to standardize and improve the treatment offered to patients and to reduce the associated social and economic burden[7]. Before establishing a community-based leg ulcer clinic in Newcastle upon Tyne a survey was performed to assess the prevalence of lower limb ulceration within the community health district and to evaluate current patterns of treatment.

Patients and methods

The prevalence and incidence of lower limb ulceration in the Newcastle Community Health District (population 240 000) was assessed using a questionnaire sent to all 70 district nurses with an active caseload at the time of the survey (May 1991) (*Table 1*). The district nurses keep accurate prospective computerized data on all the patients under their care and were able to give precise information The questionnaire also encompassed the current extent of investigation of these patients, therapeutic practices and the relative contribution of hospital specialties to their management Population information was obtained from data derived from the census of 1986 Because of the low incidence of lower limb ulceration in individuals under 45 years of age, the at-risk population was taken as those above this age and the prevalence and incidence for this group calculated

Results

The questionnaire was sent to 70 district nurses with a currently active caseload; 59 replied, a response rate of 84 per cent. The figures calculated below are based on these responses. The adult population of the Newcastle district, the prevalence of lower limb ulceration calculated for the adult population over the age of 45 years and the annual incidence for the same population, based on the number of new ulcers in the 3 months before the study, are shown in *Table 2*.

The time spent by nurses dressing leg ulcers, which does not include travelling time to and from the patient's home, is shown in *Table 3*. The average cost of one visit to dress a leg ulcer[8] has been estimated as £25 Based on this figure the annual cost of dressing ulcers by district nurses is £648 000 in the district studied. The frequency of dressing changes by nurses is shown in *Table 4* A total of 35 different types of dressing were used, of which the most common were hydrocolloid dressings, Inadine (Johnson and Johnson, Ascot, UK), Scherisorb (Smith and Nephew Medical, Hull, UK) and Kaltostat (BritCair, Aldershot, UK). The hydrocolloids and Inadine were considered by most nurses to give the best overall results. Of limbs with ulceration, 14 per cent were being treated with graduated elastic compression in the form of bandaging or stockings; all patients wearing elastic compression stockings found these difficult to apply, uncomfortable to wear, or both. Of the caseload of 206 ulcers at the time of the survey, 30 per cent had been present for <3 months, 20 per cent for 3–6 months, 15 per cent for 6–12 months, 26 per cent for 1–5 years and 9 per cent for >5 years The longest existing ulcer had been present for 54 years.

Of the patients, 175 (85 per cent) had been seen by a doctor at some time during the history of their ulcer but at the time of survey, 42 per cent of patients were being seen by their general practitioner only if requested by the district nurse. The remainder were seen regularly: 31 per cent at intervals of 3 months or less, 13 per cent at intervals of 6–12 months, and 14 per cent at intervals of >12 months. Only 35 per cent of patients with ulcers had been examined in hospital for their ulceration: 7 per cent by a vascular surgeon, 21 per cent by a dermatologist, 5 per cent by a diabetologist, and 2 per cent by other specialists.

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Table 1 *Questionnaire distributed to district nurses in the Newcastle Community Health District, May 1991*

1. How many patients with leg ulcers are you currently treating?
2. How many new patients with leg ulcers have you seen in the past 3 months?

3 How many hours per week do you spend dressing leg ulcers?

4. How often do you visit patients with leg ulcers? Please indicate number of patients in each category according to your current caseload

Daily 3 times a week Once a week
Alternate days Twice a week Less than once a week

5 Which type of dressings do you use? Please list type/number of dressings according to your current caseload

6a Who chooses the dressing?

You
General practitioner
Other (please specify)

6b. Are you limited to using certain dressings? Yes/No

If 'Yes' why?
General practitioner preference
FP10 availability
Other (please specify)

7 How many types of dressing have been used on each patient in your current caseload? Specify number in each group.

1 4
2 5
3 >5

8. Are there any dressings which you would like to use but which are unavailable to you? Please specify

9 Which dressings do you think give the best results?

10. How many patients in your current caseload apply their own dressings?

11. How many of your current patients have been seen by a doctor at any time for their leg ulcers?

12. Of the patients seen by a doctor, how often are they reviewed? Please indicate the number in each group.

Weekly Monthly 3 monthly
6 monthly 12 monthly Less than once a year

13. Has any of your patients been seen by a hospital specialist for their ulcers? Yes/No

If 'Yes' specify type of specialist and number
Vascular surgeon
Dermatologist
Diabetic clinician
Other (please specify)

14. Of the patients currently under your care, how many ulcers have remained unhealed for each of the following time periods?

<3 months 6–12 months >5 years
3–6 months 1–5 years

15. What is the duration of the longest-standing leg ulcer in your current caseload?
16. How many of the leg ulcers currently under your care are recurrent?
17. Do you think that further investigation of the underlying cause of ulceration would be beneficial to your patients?
18. How many of the patients currently under your care wear compression bandages or stockings? Please indicate type and number.
19. Do patients have any problems with compression stockings? Yes/No (if 'Yes' please specify).

20 Are there any ways in which you think leg ulcer management could be improved either in the community or hospital or both?

Table 2 *Incidence and prevalence of lower limb ulceration in the Newcastle Community Health District*

Total population*	240 000
Population aged >45 years*	107 400
No. of leg ulcers currently being treated	206
Prevalence of leg ulceration per 1000 of the population aged >45 years	1·9
New ulcers seen in the past 3 months	93
Annual incidence of leg ulceration†	3·5
Recurrent ulcers	97 (47)

Values in parentheses are percentages. *From the population census of 1986, †based on new ulcers seen in the past 3 months per 1000 of the population aged >45 years

Table 3 *Time spent by district nurses in treating leg ulcers*

Time per week spent dressing ulcers	
Total	190 h
Mean	3 h 12 min per nurse
Nurse visits	
Total no. per year	25 922
Total no. per week	498·5
Mean time spent with patient per visit	23 min

Table 4 *Frequency of dressing changes of ulcers*

Weekly frequency	
7 (i.e. daily)	7
3	28
2	35
1	27
<1	3
Total	100

Values are expressed as a percentage of all ulcers

Discussion

This survey has demonstrated that the prevalence of lower limb ulceration in the Newcastle Community Health District is 1·9 per 1000 population over the age of 45 years. It did not attempt to identify patients in hospital or other institutions (whose ulcers were not being treated by district nursing staff), and the true prevalence may therefore be slightly higher. However, this is a similar figure to that found in studies in Lothian[5] and Northwick Park[4], allowing for the slightly different age ranges used in these reports. The overall prevalence in the adult population in Lothian was 0·15 per cent, increasing to 0·36 per cent in the group over 65 years; the prevalence in the Northwick Park study was 0·18 per cent including patients under 40 years, and 0·38 per cent in those aged >40 years. Widmer[9] and colleagues in 1978 performed a survey of 4376 workers in the Basle chemical industry and found that 1·3 per cent of this group had suffered or were currently suffering from ulceration of the lower limb. This is somewhat higher than in the present study, although it did include healed ulcers, which are not studied here. Hansson *et al.*[6], in a retrospective study in Gothenberg, found the prevalence of lower limb ulceration to be 0·32 per cent, with an increasing prevalence with age, as in the Northwick Park and Lothian papers.

Half of the ulcers being treated at the time of the present survey had been present for ≥6 months and 47 per cent were recurrent, reflecting both the chronicity of ulcer disease and the need for careful prevention of recurrence once ulcers are healed. One of the major problems with studies such as this is that it is difficult to define the exact prevalence of venous and arterial ulceration because the diagnosis is imprecise; up to one-third of patients will have a combination of venous and arterial disease[10]. Cornwall *et al.*[4] investigated 117 ulcerated limbs of a total of 424 using Doppler ultrasonography and photoplethysmography, and demonstrated that 80 per cent of the ulcers showed some evidence of venous disease and a third of these had combined arterial disease. Dale *et al.*[5] found that

21 per cent of patients with ulcers had arterial disease with an ankle:brachial pressure index <0·9 However, it was still possible to examine only a proportion of all limbs with ulceration in both these studies, and the precise prevalence of venous ulceration remains unknown.

The referral patterns in Newcastle show that only 35 per cent of patients with leg ulcers were referred at any stage for specialist assessment and only 7 per cent had been examined by a vascular surgeon. Given that 80 per cent of patients will have venous disease and that some of the remainder will have isolated arterial disease, this referral figure is surprisingly low. Up to two-thirds of limbs with venous ulceration may have only superficial venous incompetence, with or without perforating vein reflux[11,12], and could be improved by superficial venous surgery. Increased referral of these patients by the general practitioner for assessment in a vascular unit should, therefore, be encouraged; indeed, most of the district nurses completing the questionnaires felt that further investigation of the patients was necessary. This has led to the development of a combined community and hospital leg ulcer clinic, run in conjunction with the district nurses. This will enable further investigation of the patients, with a view to improving their management within both the community and the hospital environment.

In this study the nursing workload caused by ulcers was considerable, with almost 200 nurse-hours per week spent in ulcer treatment and a total number of almost 26 000 visits per year Although this represents a substantial workload, the proportion of district nursing time spent treating ulcers within the Newcastle Health District was only 9 per cent, which is low compared with data from other areas, in which up to 60 per cent of district nurses' time was spent in such treatment[13]. A possible reason for this is that in the present study the time spent by each district nurse did not include that taken to travel to the patient's home, whereas the other studies have included this. Even taking this into account, however, it is difficult fully to explain the discrepancy.

Many different dressings may be applied to ulcers. The large variety currently used in this district illustrates that none confers any specific benefit over the others, though the hydrocolloids were felt by the nurses to promote healing. More important than the type of dressing employed is the use of elastic compression, with a reported healing rate of >70 per cent over a 12-week period[14], compared with only 30 per cent without compression[15]. In the present study only 14 per cent of patients with ulceration had been treated by appropriate elastic compression. This again illustrates the need for more detailed assessment of these patients along with appropriate education of the healthcare workers responsible for their treatment.

The expense of treatment of leg ulcers by community nurses alone is considerable, amounting to £648 000 in Newcastle each year. This does not include the cost of hospital investigation and treatment, the investigation and treatment of varicose veins, and money lost through sickness and sickness benefit The overall cost of chronic venous disease is therefore a considerable financial burden on the health service; improvements in the investigation and treatment of venous ulceration of the lower limb may be expected to decrease this cost.

This study highlights the need for further assessment of many patients with leg ulcers and for greater education of general practitioners and district nurses in the investigation and treatment of this condition By instituting a community leg ulcer clinic, which will be run by the district nurses with combined general practice and hospital specialist input, we hope to improve the management of lower limb ulceration.

Acknowledgements

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Role of topical lignocaine during carotid endarterectomy

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Forty carotid endarterectomies were undertaken in 34 patients. Operations were prospectively randomized to periarterial application of either 1 per cent lignocaine (n = *19) or normal saline* (n = *21), and detailed measurements taken of intraoperative pulse rate and blood pressure. Patients receiving lignocaine demonstrated a lower pulse rate, and lower systolic and mean blood pressures than those receiving placebo, with significance in relation to clamp application and shunt removal* ($P < 0.05$)*. It was particulary noticeable that patients receiving lignocaine demonstrated less intraoperative variation in pulse rate and blood pressure. Topical lignocaine stabilizes pulse rate and blood pressure during carotid endarterectomy.*

Changes in pulse rate and arterial blood pressure are known to occur both during and after carotid endarterectomy in many patients, although in the majority treatment is not required. In a study involving direct intra-arterial measurement of blood pressure, Crawford *et al.*[1] reported that both hypotension and hypertension occurred during surgery in a large proportion of patients, together with significant changes in pulse rate. These fluctuations were associated in particular with dissection in the region of the carotid sinus and clamping and declamping of the common carotid artery. It is thought that such manipulations induce stimulation of stretch receptors in the carotid arterial adventitia, leading to an increase in afferent impulses along the carotid sinus nerve; the baroreceptor reflex so produced leads to bradycardia and hypotension To prevent these effects on pulse rate and blood pressure, many surgeons routinely denervate the carotid sinus, either by division of the nerve or by intraoperative injection of local anaesthetic. However, this practice has been challenged in two recent publications[2,3], both of which concluded that injection of local anaesthetic was not only unnecessary but also potentially dangerous. The present double-blind randomized study was designed to determine whether the topical application of lignocaine exerted any beneficial or adverse physiological effects during the operative period.

Patients and methods

Thirty-four patients, all with a history of transient ischaemic attacks and proven severe stenosis, underwent 40 carotid endarterectomies under general anaesthesia. There were 25 men and nine women with a mean age of 60 (range 47–77) years

The anaesthetic technique was identical in all cases. Doses of 0·1 mg fentanyl and 10 mg droperidol were given intramuscularly 45 min before induction of anaesthesia After preoxygenation, anaesthesia was induced with a mixture of 10 mg droperidol, 0 6 mg fentanyl, 6 mg pancuronium and 8–10 mg etomidate, then maintained with 66 per cent nitrous oxide, 33 per cent oxygen and 0 5 per cent enflurane In normal practice, enflurane may or may not be needed, but it was administered to every patient in this study for the purpose of standardizing the technique Non-invasive monitoring of blood pressure, pulse, respiratory rate, tidal volume, oxygen saturation (S_{aO_2}) and end-tidal carbon dioxide was performed. End-tidal carbon dioxide was maintained at 40 mmHg and S_{aO_2} always >95 per cent.

A standard vertical incision was employed. Immediately before dissection in the region of the carotid bulb, random application of 10 ml of either 1 per cent lignocaine ($n = 19$) or normal saline ($n = 21$) was used to immerse the vessels for 2 min Injury to the carotid sinus nerve was avoided by the use of a nerve-sparing technique Before clamp application, 5000 units heparin were administered intravenously, and thereafter a shunt was used in all patients. Exclusion criteria were previous ipsilateral carotid surgery and a known allergy to lignocaine. Pulse rate and blood pressure were recorded at intervals of 2 min, specific note being made of the times of solution application, clamp application, shunt insertion, shunt removal and clamp removal. Mean values were calculated for each of the following periods· (1) initial dissection, (2) solution application; (3) after solution preclamp; (4) clamp on to shunt insertion; (5) during endarterectomy, (6) shunt removal to clamp removal, and (7) after reperfusion Note was made of any drug given to treat extremes of pulse rate or blood pressure during surgery Comparison of results was made using the Mann–Whitney *U* test

Results

Overall mean values comparing pulse rate between the two groups are shown in *Figure 1*. In the lignocaine group most values are lower, with significant differences ($P < 0.05$) during periods 3, 4 and 6. It is also seen that in the lignocaine group systolic arterial pressure tended to be lower, these differences being significant during periods 4 and 6 (*Figure 2*). Similarly, mean arterial pressure in the lignocaine group was significantly lower at periods 4, 5 and 6 (*Figure 3*). Therefore, patients receiving topical lignocaine had a stable pulse rate and arterial pressure throughout the duration of surgery, whereas those receiving placebo experienced fluctuations, particularly in association with clamp application before shunt insertion and after its removal. Severe bradycardia requiring treatment with intravenous atropine occurred in three patients in the placebo

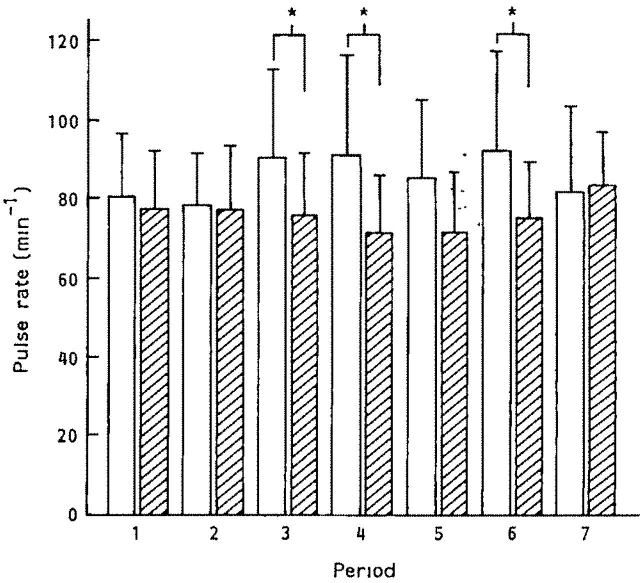

Figure 1 *Mean(s.d.) pulse rate during surgery* ▨, *Lignocaine,* ☐, *placebo.* *$P < 0.05$ (*Mann–Whitney* U *test*)

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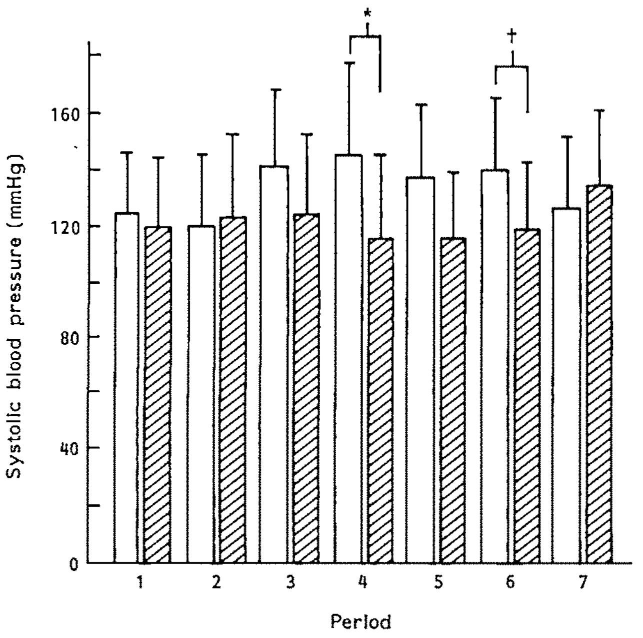

Figure 2 *Mean(s.d.) systolic blood pressure during surgery* ■, *Lignocaine*, □, *placebo* *$P < 0.05$, †$P < 0.02$ (*Mann–Whitney* U *test*)

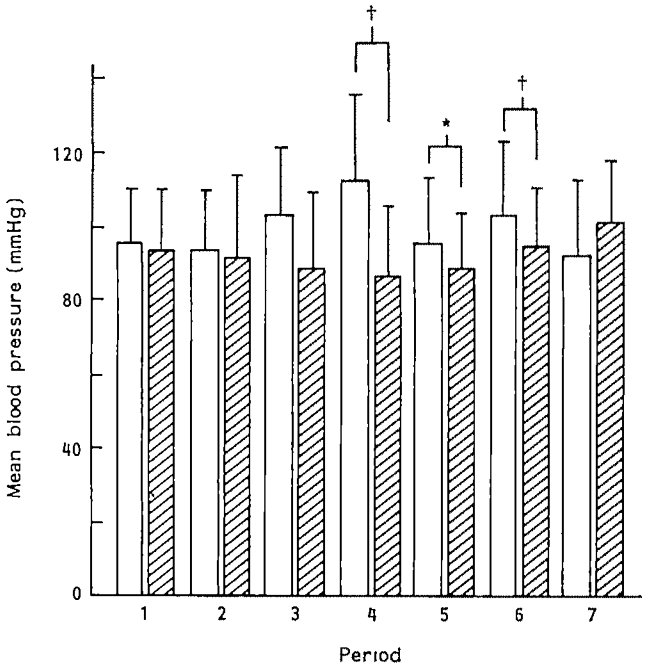

Figure 3 *Mean(s.d.) mean blood pressure during surgery* ■, *Lignocaine*, □, *placebo*. *$P < 0.05$, †$P < 0.02$ (*Mann–Whitney* U *test*)

group, although in one this was before solution application; one of these patients also required methoxamine for associated hypotension. No such effects were seen in patients receiving lignocaine.

Discussion

Most reports in the literature describing what happens to pulse rate and blood pressure in patients undergoing carotid endarterectomy concentrate mainly on the immediate period after operation[1,4–9], when hypertension is common and is associated with a 10–47 per cent incidence of fixed neurological deficits or death if allowed to persist[6,7,10,11]. Towne and Bernhard noted that the first indication of neurological problems in the recovery room was the development of significant hypertension as the patient emerged from the effects of anaesthesia, and that this hypertension usually preceded any neurological deficits[7]. They also found that preoperative hypertension was the single most important determinant of the development of hypertension after operation. Such patients respond more easily to pain, hypercarbia, hypothermia and other sequelae of 'emergence excitement' known to cause hypertension after operation[5]. Indeed, untreated hypertension constitutes a serious risk to patients undergoing general anaesthesia for any kind of surgery[12]. An important cause of hypertension after carotid endarterectomy is thought to be denervation of the carotid bulb resulting in abolition of the baroreceptor reflex. Angell-James and Lumley, measuring electroneurograms from the carotid sinus nerve, demonstrated a correlation between nerve activity and blood pressure, two patients with decreased nerve activity developing hypertension[13]. Towne and Bernhard[7] reported that there was no difference in the incidence of hypertension after operation whether or not patients underwent nerve preservation or denervation; since routine injection of lignocaine into the carotid bifurcation was practised, such similarity between the two groups is hardly surprising

Hypotension after carotid endarterectomy is also common, with a reported incidence of 26–50 per cent[4,8], and may be associated with neurological deficits[6]. It is thought that this hypotension reflects normal carotid sinus activity, since before surgery rigid atheromatous plaques are thought to damp pressure waves reaching the sinus baroreceptors, whereas after surgery unimpeded exposure to pressure waves may result in an exaggerated hypotensive response. Tarlov *et al.* reported that this could be prevented by carotid sinus denervation[4], although temporary denervation by infiltration of the carotid bulb adventitia with 1 per cent lignocaine was thought to be safer by allowing time for baroreceptor 'resetting' while not permanently abolishing what is a normal physiological mechanism[9]. It has also been suggested that control might be implemented further into the period after operation by leaving a catheter in the wound for intermittent additional infiltration[8]

It appears, therefore, that baroreceptors located in the adventitia of the carotid bulb may be intimately involved in variations of arterial pressure seen during and after carotid endarterectomy First described by Hering[14] in 1923, the normal response of these receptors is to induce reflex hypotension and bradycardia in response to stretch[15], although if the stimulus remains constant activity in the nerve gradually diminishes[16] Baroreceptor sensitivity to stimulation by intravenous agents such as phenylephrine or angiotensin II has been shown to be decreased in patients who are elderly[17], hypertensive[18–20] or have acute and chronic cerebrovascular disease[21]. This decreased sensitivity may be due to loss of compliance in the atheromatous arterial wall, with increased elasticity after endarterectomy resulting in a strong baroreceptor reflex. As well as causing hypotension, stimulation of baroreceptors has a negative inotropic effect on the heart, causing decreased left ventricular output and increased mean left atrial pressure[22]. Pickering *et al.* studied the effect of autonomic blockade on baroreceptor function in humans; sympathetic blockade produced reflex sensitivity which was increased at rest and normal after exercise, whereas parasympathetic blockade virtually abolished the reflex both at rest and exercise[23]. These results suggested that reflex bradycardia following a rise in blood pressure was largely vagal in origin and that increased sympathetic tone of exercise may block parasympathetic changes.

To avoid wide variations in arterial pressure during and after carotid endarterectomy, Cafferata *et al.* recommended both a nerve-sparing dissection and treatment of hypotension with 2-ml boluses of topical 2 per cent lignocaine or intravenous pressor drugs[8]. Our practice is to fill the wound with a solution of 1 per cent lignocaine and leave this to bathe the vessels for 2 min. Since we do not directly infiltrate the carotid sinus it is possible that there may be some direct effect on the vagus nerve. Unlike previous authors, we have obtained measurements of pulse rate and blood pressure at regular intervals throughout surgery, and those patients receiving lignocaine demonstrated significant differences in both pulse rate and blood pressure at certain crucial points, namely in relation to clamp application before insertion and removal of the shunt. However, contrary to the expected rise, pulse and blood pressure were lower in the group receiving lignocaine. This is difficult to explain but may reflect a stabilizing effect; marked individual fluctuations occurring in patients receiving placebo produced higher mean values overall. An important reason for using topical lignocaine has been the occurrence of severe bradycardia during dissection; no evidence of this has been seen after lignocaine application and the results of this study support the use of this technique.

Barman *et al.* reported significantly greater changes in blood pressure in patients receiving lignocaine *versus* saline, but only obtained measurements every 2 min for a 10-min period before clamp application[3]. They did not study what happened during the critical period after clamp application, nor report the incidence of postoperative hypotension or hypertension. Therefore, their conclusion that lignocaine application might be detrimental to perioperative blood pressure is based on only a 10-min period of observation. In a much larger prospective randomized study, Elliot *et al.* injected the carotid sinus nerve with bupivacaine[2]. Pulse and blood pressure were measured only at 5 and 30 min after injection, but the exact stage of the operation at these 'random' time points is not clear. On the basis of these two measurements they found an incidence of intraoperative hypertension of 63 per cent in patients receiving bupivacaine, twice that of controls, and concluded that local anaesthesia of the carotid sinus nerve is of no benefit and potentially detrimental. However, the present study has shown that topical lignocaine application abolished intraoperative fluctuations in pulse and blood pressure associated with arterial manipulation and clamping

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Diagnostic and therapeutic aspects of fine-wire localization biopsy for impalpable breast cancer

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During the first 2 years (July 1989 to July 1991) of the Avon Breast Screening Service, fine-wire localization biopsy was indicated in 213 impalpable breast lesions. A total of 144 lesions were benign and 69 malignant. Only four of 213 lesions (1·9 per cent) were not excised at the first localization. Factors influencing reoperation in the 69 patients with malignant impalpable lesions were examined. There was a significant association ($P < 0{\cdot}001$) *between parenchymal disturbances on mammography and invasive carcinoma, and between non-invasive carcinoma and microcalcification* ($P < 0{\cdot}001$)*. In 31 patients the localization biopsy was the only surgical procedure. Thirty-eight patients required further surgery: 12 underwent further local excision and 26 mastectomy. Reoperation was more frequent in patients with calcification than in those with parenchymal disturbance* ($P < 0{\cdot}001$)*. The most frequent indications for mastectomy were inadequate excision of widespread comedo ductal carcinoma* in situ *or invasive ductal carcinoma combined with extensive ductal carcinoma* in situ. *Fine-wire localization biopsy was a combined therapeutic and diagnostic procedure in 31 of 69 women with impalpable screen-detected lesions. The majority of patients required further surgery because radiological abnormalities underestimated the extent of disease.*

The Forrest report[1] predicted that the UK breast screening project would result in 15 000 biopsies per year. It has been estimated[2] that 40 per cent of these lesions would be impalpable and require radiographic localization to guide surgical excision. Early localization methods included skin marking[3] and the injection of radio-opaque material combined with tissue dyes[4]. Most screening centres now use a variant of the self-retaining hooked needle first described by Frank *et al*[5]. Needle localization has resulted in the excision of the radiographic abnormality at the first operation in 94–99 per cent of cases[6,7] and is now a well described and widely practised diagnostic technique. As the biopsy may allow total excision of the suspicious lesion, it may amount to a 'wide excision' and be therapeutic. All fine-wire localization biopsies of impalpable lesions detected during the first 2 years of screening in Avon were reviewed to examine the surgical sequelae in patients with malignant lesions.

Patients and methods

During the first 2 years (July 1989 to July 1991) of the Avon Breast Screening Service, 46 278 women were invited to attend for single-view mammography, 31 114 (67·2 per cent) accepted. A total of 174 carcinomas were detected (6 per 1000 women screened). The overall benign:malignant ratio was 1:1. Stereotactic fine-needle aspiration cytology was not then available and, although ultrasonography was used to guide aspiration cytology for some larger lesions, the majority of impalpable lesions required localization for histological diagnosis. Fine-wire localization biopsy was performed on 213 radiologically suspicious lesions.

Over the 2 years of the study a number of refinements and changes in the basic techniques occurred; the methods described were used in the majority of patients. Localization was carried out on the day of operation. During the first 18 months, lesions were localized using the cross lights technique[8] with a grid reference plate on the Mammomat 2 Unit (Siemens, Erlangen, Germany). The stereotactic biopsy attachment (Siemens) was used during the final 6 months for preoperative localization[9]. The first 150 lesions were localized with the Mammolok wire (Henley's Medical Supplies, Welwyn Garden City, UK); Percuguides (Mediplus, Bourne End, UK) were used in the latter part of the series.

Excision of the lesion guided by the wire was performed under general anaesthesia and the orientation of the specimen indicated with a series of sutures. The operative specimen was placed in a Dubin device (E-z-em, London, UK), a plastic container with an internal fitting that enables compression to be applied during specimen radiology. The specimen was radiographed in a bench top specimen radiology unit, the Micro 50 Specimen Radiography system (Microfocus Imaging, Hammond, Indiana, USA), within the Dubin device. After the surgeon had seen the images and was satisfied that the original radiological abnormality had been excised, the surgical incision was closed. The compression in the Dubin device was released and the container filled with 10 per cent formal saline.

All specimens were reviewed by the same two pathologists and after the first 12 months all impalpable screen-detected lesions were processed by the South-West Regional Breast Pathology and Quality Assurance Unit. After formalin fixation for 48 h, the specimen was dried, weighed, macroscopically described and differentially marked with coloured gelatins[10]. The specimen was then sliced at 2-mm intervals[11] and the slices laid sequentially in a compartmentalized plastic box for radiographic examination. The material to be processed was selected on the basis of macroscopic and radiological appearances. An average of four blocks were taken for each specimen and processed in a standard fashion[12]. The histopathology report for each lesion included the presence and type of non-invasive and invasive disease, the size or extent of the lesion, the grade of invasive ductal cancers[13], and the margins of excision.

The radiographs and histological slides of all patients requiring surgical intervention were discussed at monthly audit meetings attended by the screening centre radiologists, histopathologists and surgeons. The adequacy of surgical and adjuvant treatment of each patient was reviewed in the light of the radiographic extent of disease, the type and extent of pathology, and the margins of excision. During the period of this audit national protocols for patient management were being developed. None of these patients was entered into a trial. The final decision on the extent of surgery and type of adjuvant treatment was made by the surgical consultant in discussion with each patient.

The data cited in this paper come from the records of the Regional

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Breast Pathology and Quality Assurance Unit and the Bristol Royal Infirmary Department of Surgery breast cancer database. Statistical analysis was performed using the χ^2 test with Yates' correction for small numbers.

Results

Of the 31 114 women who accepted mammographic screening, 212 had radiologically suspicious lesions that were impalpable on clinical examination. One patient had bilateral lesions requiring localization; fine-wire localization was therefore performed in 212 women for 213 lesions. The lesion was excised at the first operation on 209 occasions; four patients required a second operation. In three patients with microcalcification there was inaccurate needle placement, poor-quality specimen radiographs, and the lesion was missed at the first operation A second localization biopsy was successful in all three; two had benign pathology and one a focus of ductal carcinoma *in situ* (DCIS) that was completely excised. In one patient the lesion was thought to be palpable and localization was therefore cancelled; the mammographic abnormality persisted and the lesion (a lipoma) was eventually retrieved by fine-wire localization biopsy.

There were 144 benign and 69 malignant lesions, giving a benign:malignant ratio of 2.1 for the impalpable lesions. *Table 1* lists the histological diagnosis for the benign lesions, nearly 70 per cent of which were benign fibrocystic disease or fibroadenoma. The largest single group of benign lesions was benign fibrocystic disease, 18 per cent of which showed epithelial atypia. Complex sclerosing lesions and involutional breast tissue were common reasons for biopsy. The term 'involutional breast' refers to a radiological opacity that may be palpable[14] and which is due to an island of dense normal breast tissue within a more radiolucent involuted background[15].

Table 1 *Histological diagnosis for benign lesions*

Diagnosis	No
Benign fibrocystic disease	49 (34·0)
Benign fibrocystic disease with atypia	11 (7·6)
Fibroadenoma	40 (27·8)
Complex sclerosing lesion	15 (10·4)
Involutional breast	13 (9·0)
Hamartoma	4 (2·8)
Duct papilloma	3 (2·1)
Lymph node	2 (1·4)
Adenoma	1 (0·7)
Benign phylloides	1 (0·7)
No specific lesion	5 (3·5)
Total	144 (100)

Values in parentheses are percentages

Table 2 *Histological diagnosis for malignant lesions*

Diagnosis	No.
In situ	
DCIS	22 (32)
LCIS	1 (1)
DCIS with microinvasion	6 (9)
Invasive	
Invasive ductal	24 (35)
Invasive ductal with extensive DCIS	10 (14)
'Special'	
Invasive lobular	2 (3)
Mucoid	1 (1)
Papillary	1 (1)
Tubulolobular	1 (1)
Tubular	1 (1)
Total	69 (100)

Values in parentheses are percentages. DCIS, ductal carcinoma *in situ*, LCIS, lobular carcinoma *in situ*

Table 2 shows the histological diagnosis for the malignant lesions. Forty-one per cent were non-invasive: 28 DCIS and one lobular carcinoma *in situ*. Six patients had DCIS with microinvasion. A total of 49 per cent of malignant lesions were invasive ductal carcinoma (IDC) of no specific type; of these, ten (29 per cent) were associated with extensive DCIS. There were two invasive lobular carcinomas and four 'special' or low-grade invasive lesions.

The mammographic abnormalities were divided into three categories: microcalcification only; parenchymal disturbance, such as irregular or ill-defined opacities, stellate lesions and architectural distortion; and mixed lesions with parenchymal abnormalities combined with microcalcification. The type of radiographic abnormality was not helpful in predicting whether a lesion was benign or malignant because there was no significant difference in the distribution of benign and malignant disease for each mammographic abnormality (*Table 3*). However, in the malignant cases, when the radiological classification was simplified into two groups (calcification and parenchymal disturbances), there was a strong correlation of calcification with non-invasive carcinoma (*Table 4*). Invasive carcinoma occurred much more commonly with parenchymal disturbances ($P < 0\cdot001$).

Thirty-one patients underwent fine-wire localization biopsy as the only procedure A total of 35 had two operations: the initial guided biopsy was followed by wider excision in 12 women and mastectomy in 23. Three patients underwent three procedures: two local excisions (including the first guided one) followed by mastectomy.

There was no difference in the size of IDCs completely excised at fine-wire localization biopsy and those requiring further surgery. The mean(s.d.) size of the IDCs treated by fine-wire localization biopsy was 11·6(5·4) mm and that of the lesions requiring another procedure 11·8(3·4) mm.

Table 5 shows the relationship between mammographic abnormality and the number of surgical procedures. Patients with calcification required further surgery significantly more often than those with parenchymal disturbances ($P < 0\cdot001$).

Table 3 *Mammographic abnormality in relation to pathology*

Pathology	Calcification	Parenchymal disturbance	Mixed
Benign	59 (63)	75 (72)	10 (62)
Malignant	34 (37)	29 (28)	6 (38)

Values in parentheses are percentages

Table 4 *Relationship between radiology and malignant subgroups*

Radiology	Non-invasive	Invasive
Parenchymal disturbance	5	23
Calcification with or without parenchymal change	29	8

Four cases with 'special' histological type (*Table 2*) are excluded Yates' $\chi^2 = 21\cdot04$, 1 d.f., $P < 0\cdot001$

Table 5 *Relationship between radiology and number of surgical procedures*

Mammographic abnormality	1 operation	> 1 operation
Parenchymal disturbance	22	6
Calcification with or without parenchymal change	9	32
Total	31	38

Yates' $\chi^2 = 19\cdot33$, 1 d.f., $P < 0\cdot001$

Table 6 *Pathology related to final surgical procedure*

	Breast conservation	Mastectomy
Non-invasive carcinoma	19	20
Invasive carcinoma	24	6
Total	43	26

Yates' $\chi^2 = 8{\cdot}79$, 1 d.f., $P < 0{\cdot}01$

Table 6 relates the pathology to the final surgical procedure. Fifty per cent of the predominantly non-invasive lesions were ultimately treated by mastectomy and the majority of invasive ductal tumours by conservative surgery. A total of 16 (67 per cent) of the patients with IDC have had one surgical procedure. Of these, six underwent axillary node sampling at the time of localization: two had frozen sections confirming invasive disease and the other four had upper outer quadrant stellate lesions on mammography that were suspicious of malignancy and axillary sampling was carried out through the same incision. Only one of six axillary samples was positive. Of the 16 patients with IDC who have undergone one surgical procedure, ten received adjuvant radiotherapy and 13 received adjuvant tamoxifen. The three patients who did not receive tamoxifen had proven negative nodes.

Patients who had clear margins of <5 mm or incomplete excision of malignant lesions at fine-wire localization biopsy were offered further surgery. Women with DCIS or IDC were given the choice of breast conservation or mastectomy. The three patients undergoing three operations all had extensive comedo DCIS without invasion. Mastectomy was recommended after *in situ* disease extended to the margins at the second attempt at local excision. All three had residual DCIS in the mastectomy specimen

Discussion

Before the introduction of widespread breast screening, clinical experience in the management of mammographically detected impalpable breast carcinoma was limited. The publication of the draft guidelines[16] for surgical quality assurance in the National Health Service Breast Screening Programme in August 1991 prompted a review of the results of the first 2 years of operation of the Avon Breast Screening Unit. The compliance rate of 67 per cent fell just short of the expected 70 per cent but other parameters (e.g. number of cancers detected per 1000 women screened, overall benign malignant ratio) were within the objectives of the screening programme

In this series, four of 213 lesions (1·9 per cent) were missed at the first operation, a figure that compares favourably with those in the literature[6,7] Some experienced centres have missed 5–10 per cent of mammographic abnormalities[17] All the missed lesions in the present study occurred in the first year. Later refinements in the techniques of excising and processing lesions included the use of the compression device for the initial specimen radiology, and the specialized breast pathology service. Compression improves the quality of radiology and having the specimen fixed in the device preserves its orientation. Great care has been taken by the pathologist to localize the radiographic abnormality within the resected specimen before choosing the tissue to be processed The original and specimen radiographs have been reviewed together to make sure the correct breast tissue has been excised and examined histologically.

Benign fibrocystic disease and fibroadenoma accounted for a high proportion of the benign lesions. Benign fibrocystic disease with atypia forms an important subgroup of benign lesions as the atypical hyperplasias are associated with an increased risk of development of invasive cancer[18] Patients with this diagnosis are therefore offered annual follow-up mammography. Of the 144 benign lesions, 11 showed atypical hyperplasia, a lower proportion than observed by others[19,20]. With the introduction of stereotactic fine-needle aspiration a reduction in the number of biopsies of benign lesions such as benign fibrocystic disease and involutional breast is anticipated. It is difficult to eliminate biopsies of complex sclerosing lesions as they are highly suspicious radiologically and often have significant cytological atypia[21]. These lesions are often large, seldom palpable and rarely seen in symptomatic patients.

In this series the number of 'special' types of carcinoma, including lobular carcinoma, is lower than expected[14] and previously reported[19]. This may be because all invasive tumours were extensively sampled and the criteria for the diagnosis of the special types laid down by The Royal College of Pathologists[22] strictly followed.

The benign·malignant ratio of mammographically detected impalpable lesions in this series was 2:1, consistent with those reported by other centres[23,24]. The type of radiological abnormality was not helpful in predicting the likelihood of malignancy. Microcalcification with or without a parenchymal element was more commonly associated with non-invasive carcinoma, and parenchymal abnormality alone was more frequently seen with invasive disease. In the majority of patients with parenchymal abnormalities and invasive carcinoma, complete excision was achieved during fine-wire localization biopsy and further surgery not performed. Adjuvant radiotherapy and tamoxifen after operation were recommended. In patients with malignant disease associated with microcalcification, the mammographic appearances often underestimated the extent of non-invasive ductal carcinoma. Further surgery was required and in almost 50 per cent of this group mastectomy was performed

Fine-wire localization biopsy is widely regarded as the definitive diagnostic procedure for impalpable mammographically detected breast abnormalities. Some have advised strongly against its use as a therapeutic procedure[25] because of incomplete excision or inadequate margins, particularly in patients with *in situ* carcinoma. This study suggests that fine-wire localization biopsy should be primarily diagnostic for calcified lesions and that further surgery will be required in most patients. Wobbes *et al.*[26] advocated mastectomy for all patients with DCIS because of the high number with residual disease following conservative surgery, although such disease was confined to one quadrant of the breast in two-thirds of women. The management of DCIS remains controversial; the quality assurance guidelines[16] recommend that patients with DCIS should be entered into national trials

Patients with malignant disease associated with parenchymal disturbances alone are likely to have IDC or a 'special' type of tumour (tubular, mucoid, papillary etc.) These special tumours are known to have a better prognosis[27]. One of the quality assurance guidelines is to avoid the overtreatment of patients with favourable lesions

Breast conservation is now an acceptable alternative to mastectomy for IDC in symptomatic women, particularly for small tumours. The optimal margin of excision for invasive cancers is unknown. If a special type or low-grade invasive ductal cancer has been completely excised by fine-wire localization biopsy, further surgery to the breast may not be necessary or justified Stereotactic fine-needle aspiration cytology should identify more malignant lesions before operation and may permit planning of formal segmentectomy and complete excision of well defined carcinomas using localization techniques. The use of frozen section in the pathological processing of impalpable lesions is generally not recommended[25,28], although some authors[19,20,23] have found it helpful. In two patients with IDC, the additional information provided by frozen section led the surgeon to carry out a wider excision and axillary node sample at the first operation.

The recommended biopsy size[16] for benign lesions is <20 g. The object of this recommendation is to limit the amount of biopsy tissue to ensure good cosmesis, particularly in women with benign disease. Many factors, such as the size and depth of the lesion and size of the breast, determine the amount of tissue excised by the surgeon Specimens were not routinely weighed until late in this series. The mean(s.d.) weight of 54 benign biopsies was 38(24) g and of 17 malignant cases 55(30) g. The cosmetic results were not formally assessed but, despite the biopsy size being larger than recommended, appeared satisfactory. The psychological effects of multiple interventions must be balanced against a good cosmetic result, and the anxiety generated by multiple investigations and surgical procedures should not be underestimated. Studies have shown that the time from discovery to treatment is the most stressful period for many patients with breast cancer[29,30] and women undergoing breast biopsy are more anxious than those undergoing definitive surgery for diagnosed breast cancer[31,32].

The primary objective of the use of fine-wire localization biopsy is to provide a histological diagnosis for a suspicious impalpable mammographic abnormality. In some patients complete excision will be achieved at the same operation. If combined with radiotherapy and adjuvant therapy, further surgical intervention may be inappropriate. Further audit and clinical trials will be necessary to elucidate the optimal treatment for *in situ* and small screen-detected cancers.

The British Association of Surgical Oncology (BASO) is now recruiting patients with breast cancer into three randomized clinical trials. Two of these will examine the effects of adjuvant therapy on recurrence in the treated breast in patients who have undergone complete local excision of DCIS or small low-grade IDCs. The third will look at the effect of tamoxifen on the contralateral breast in patients with DCIS treated by mastectomy. Knowledge gained from the BASO trials and audit of working practice within the breast screening service should modify and refine the quality assurance guidelines.

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Needle core biopsy of the breast with a spring-loaded device

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Over a 2-year period, 151 outpatients with a palpable breast lump requiring needle core biopsy were randomized to a Tru-Cut 14-G (T14), Bioptycut 14-G (B14) or Bioptycut 18-G (B18) needle. Use of a Biopty gun resulted in less pain than a Tru-Cut needle. An inadequate sample was obtained after two needle passes in 11 of 49 (T14), none of 51 (B14) and two of 51 (B18) patients ($\chi^2 = 14{\cdot}6$, 2 d.f., P = 0·0007). Tissue samples were assessed by a single pathologist for tissue volume and overall diagnostic value; the B14 group scored better than the B18 and T14 for both of these parameters (P < 0·003). The sensitivities were 68 (T14), 88 (B14) and 96 (B18) per cent (overall $\chi^2 = 7{\cdot}3$, 2 d.f., P = 0·026). The Biopty gun with a 14-G needle results in a higher sampling success rate, greater diagnostic sensitivity and a better specimen quality than the Tru-Cut, and is much easier to use.

Accurate non-operative tissue diagnosis is essential in patients with breast disease. In benign conditions it reduces the need for open biopsy, and in cases with malignancy obviates the need for frozen section and allows preoperative counselling and planning of treatment Fine-needle aspiration cytology (FNAC) is the principal method of obtaining a tissue diagnosis in specialist centres[1–5]; needle core biopsy can be relied on in centres without expertise in FNAC[6–9]. A small proportion of patients with breast cancer still require needle core biopsy to obtain a tissue diagnosis.

Needle core biopsy of very hard or very soft lesions of the breast with a Tru-Cut needle (Travenol Laboratories, Deerfield, Illinois, USA) can be difficult, and small lesions (<2 cm in diameter) present problems[10]. The need for two hands to operate a Tru-Cut needle makes it difficult simultaneously to localize and fix the lump Uncoordinated movement of the two parts of the Tru-Cut needle results in either no sample or tissue distortion, which reduces the usefulness of the sample for histological diagnosis

The use of a spring-loaded device such as the Biopty gun (Bard, Crawley, UK) to fire the biopsy needle offers advantages· the double-spring mechanism gives a precise and coordinated cutting action, and the one-handed operation frees the other hand for localization of the lump. Its utility in renal[11], abdominal mass[12] and prostatic[13] biopsy is well described, but its value in the diagnosis of breast lumps has not been compared with that of Tru-Cut

Patients and methods

During the period of this study, FNAC was not used From September 1989 to August 1991, 151 consecutive outpatients with palpable breast lumps (*Table 1*) were randomized to percutaneous biopsy using either a Tru-Cut 14-G (T14 group), a Bioptycut 14-G (B14 group) or a Bioptycut 18-G (B18 group) needle. Bioptycut needles were used with the Biopty gun (*Figure 1*), an automated device that produces a 17-mm long tissue core The Tru-Cut needle produces a 20-mm long tissue core. In all patients, the skin and subcutaneous tissue were infiltrated with 2 ml 1 per cent lignocaine with adrenaline and the skin punctured with the point of a small scalpel blade (no 11) A standard technique was used for the Tru-Cut[14]. The surgeon was allowed two passes with the needle allocated by randomization If an inadequate specimen was obtained, a different needle type was used in a cross-over design, and the subsequent sample sent separately for histological examination Patients were assessed for pain resulting from the biopsy using a standard four-point descriptive scale (0, none, 1, mild, 2, moderate; 3, severe).

The paraffin sections of the biopsy specimens were evaluated by a single pathologist (A M L.) without knowledge of the needle type used

Table 1 *Details of the three biopsy groups*

	Tru-Cut 14 G	Bioptycut 14 G	Bioptycut 18 G
No of patients	49	51	51
Median (range) age (years)	57 (24–78)	50 (24–79)	56 (20–87)
Consultant·registrar ratio	3 5 1	3·3 1	4 1·1
No of carcinomas	25	24	24
Median (range) case record follow-up (months)	11 (1–24)	11 (1–24)	11 (1–24)

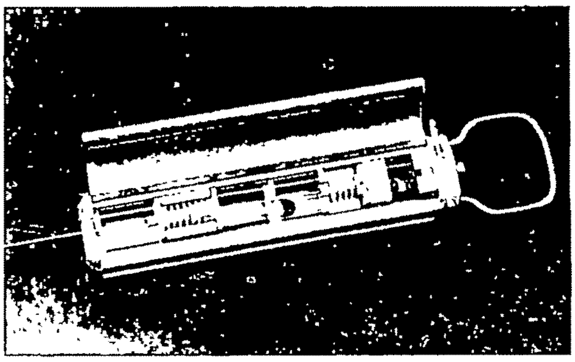

Figure 1 *The Biopty gun (hinged flap open) loaded with a Bioptycut needle*

Each sample was scored on a scale of 0–4 for volume of tissue and overall diagnostic value This scoring system was developed by retrospective assessment of 60 needle core biopsy samples (20 of each needle type) taken before the start of the present study. The sample volume was calculated from measurement of the length and diameter of each fragment and scored according to the following scale. 4 for any volume >15 2 mm^3, 3 for 8 7–15 2 mm^3, 2 for 5 8–8 6 mm^3, 1 for 2 3–5 7 mm^3, and 0 for any volume ⩽2 2 mm^3 The diagnostic value of each specimen was graded 0 for inadequate, 1 for poor, 2 for average, 3 for good and 4 for excellent.

Mammography was performed routinely before needle biopsy in patients >35 years old. Only those with benign lesions on the diagnostic triad of clinical examination, mammography and needle core biopsy did not proceed to surgery The definitive clinical diagnosis was obtained by examination of the case records a median of 11 (range 1–24) months after the biopsy date Sensitivity, specificity, false-positive

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rate and accuracy were calculated using standard formulae[5]. The final clinical diagnosis at follow-up was taken as the definitive diagnosis for patients who did not subsequently undergo surgery.

For statistical analysis, the χ^2 test with Bonferroni correction for intergroup comparisons was applied to ratios, the Kruskal–Wallis test with follow-up by the Mann–Whitney *U* test (with Bonferroni correction) for intergroup comparisons was applied to scores.

Results

The groups were well matched for age, proportion of malignant lesions, surgeon performing biopsy, and case record follow-up period (*Table 1*). Pain scores recorded immediately after the biopsy are shown in *Figure 2*. B18 patients experienced significantly less pain (Kruskal–Wallis $\chi^2 = 9{\cdot}2$, 6 d.f., $P = 0{\cdot}01$; Bonferroni-corrected Mann–Whitney *U* test, $P = 0{\cdot}04$) than the T14 group. There was a trend towards lower pain scores ($P = 0{\cdot}05$, uncorrected Mann–Whitney *U* test) in the B14 compared with the T14 group.

There was no major complication. Troublesome bleeding occurred in three patients in the B14, two in the B18 and one in the T14 group. Minor bruising was common in all three groups; no patient developed pneumothorax.

The Biopty gun was more reliable in producing an adequate sample; after two passes with the needle, an inadequate sample was obtained from 11 of 49 patients in the T14 group, compared with two of 51 in the B18 group, and none of 51 in the B14 group ($\chi^2 = 14{\cdot}6$, 2 d.f., $P = 0{\cdot}0007$). An adequate biopsy was subsequently obtained from the 11 patients in the T14 group by using a Bioptycut 14 G, and in the two patients in the B18 group by using a Tru-Cut needle.

The Bioptycut 14-G needle produced specimens of larger volume and better diagnostic value than either the Bioptycut 18-G or Tru-Cut 14-G needle (Kruskal–Wallis $\chi^2 = 22$ and 18, respectively, 8 d.f., $P < 0{\cdot}0001$; Bonferroni-corrected Mann–Whitney *U* test, $P < 0{\cdot}005$ for all comparisons). The scores are shown in *Figures 3* and *4*. There was no significant difference in the volume or diagnostic value scores between the B18 and T14 groups.

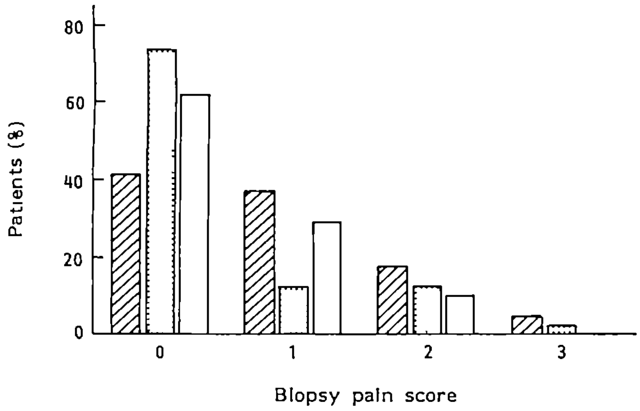

Figure 2 *Pain scores of the patients in the three biopsy groups.* ■, *Tru-Cut 14 G,* ⬚, *Bioptycut 18 G,* □, *Bioptycut 14 G*

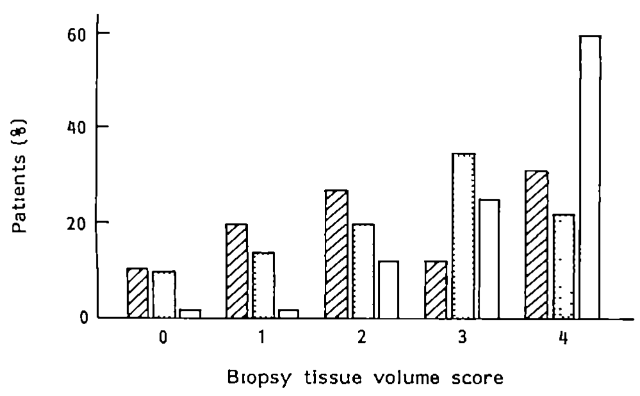

Figure 3 *Tissue volume scores of the biopsy specimens from the three biopsy groups.* ■, *Tru-Cut 14 G,* ⬚, *Bioptycut 18 G,* □, *Bioptycut 14 G*

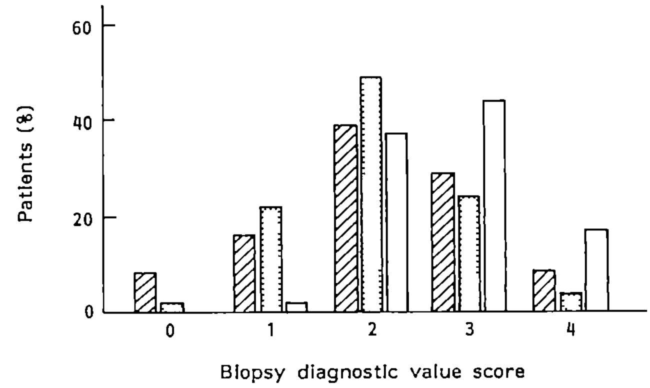

Figure 4 *Diagnostic value scores of the biopsy specimens from the three biopsy groups* ■, *Tru-Cut 14 G,* ⬚, *Bioptycut 18 G;* □, *Bioptycut 14 G*

Table 2 *Diagnostic accuracy of the three biopsy groups*

	Tru-Cut 14 G	Bioptycut 14 G	Bioptycut 18 G	Bioptycut 14 G and 18 G
True positive (*n*)	17	21	23	44
False negative (*n*)	8	3	1	4
True negative (*n*)	24	27	27	54
False positive (*n*)	0	0	0	0
False-negative rate (%)	24	10	4	7
Sensitivity (%)*	68	88	96	92
Specificity (%)	100	100	100	100
Accuracy (%)	84	94	98	96

*Sensitivity: overall $\chi^2 = 7{\cdot}3$, 2 d.f., $P = 0{\cdot}026$, T14 *versus* B14, $\chi^2 = 2{\cdot}7$, 1 d.f., $P = 0{\cdot}10$ (0·31), T14 *versus* B18, $\chi^2 = 6{\cdot}3$, 1 d.f., $P = 0{\cdot}012$ (0·036); B14 *versus* B18, $\chi^2 = 1{\cdot}1$, 1 d.f., $P = 0{\cdot}30$ (0·89), *P* values are the result of χ^2 tests without (with) a Bonferroni correction

The diagnostic accuracy of the three needle types is shown in *Table 2*. The B18 group had a significantly higher sensitivity than the T14 group (96 *versus* 68 per cent, $\chi^2 = 6{\cdot}3$, 2 d.f., $P = 0{\cdot}036$ with Bonferroni correction), but the difference between the B14 group (88 per cent) and the other two groups was not significant. Three of the false negatives in the T14 group were caused by an inadequate sample being produced after two needle passes. In two of these three patients, subsequent biopsy with a 14-G Bioptycut needle was positive. The one false negative in the B18 group was the result of an inadequate sample being obtained after two needle passes; a positive diagnosis was subsequently obtained with a 14-G Tru-Cut needle.

Discussion

The sensitivity of Tru-Cut in this study (68 per cent) is towards the lower end of the range of reported results (67–95 per cent)[4,6–10,15–18]. This was in part because of the study design, which allowed only two attempted needle passes with the randomized needle; three of the false negatives were caused by no sample being produced after two needle passes. A strong relationship between operator experience and the quality and adequacy of the specimen occurs in FNAC of the breast[2,19,20]. The same is likely to be true of needle core biopsy with the Tru-Cut. The fact that the 49 Tru-Cut biopsies over 2 years were performed by eight different surgeons may have contributed to the poor result in this group. Excellent results were obtained with the Biopty gun (absolute diagnostic sensitivity 92 per cent), suggesting that this technique is less dependent on operator experience

The Bioptycut device was first developed by Lindgren in 1982 for use in ultrasonographically guided renal biopsy[11] and extended to ultrasonographically guided biopsy of abdominal masses[12] and prostate[13]. Barreto *et al.*[21] reported the use of the Biopty gun with an 18-G needle in 107 patients with suspected early breast cancer, with a sensitivity of only 65 per cent. The apparently poor results were partly due to lack of previous experience and to including only patients with early disease.

Brun Del Re developed a spring-loaded biopsy pistol to hold a Tru-Cut needle[22]. This device has a single spring action that fires the cannula part of the needle. Bradbeer reported its use in a series of 194 patients with palpable breast lumps[6], and histological examination of frozen sections gave a sensitivity of 89 per cent and specificity of 96 per cent. Others abandoned this device because patients found it disconcerting[18].

The Biopty gun has been shown to be effective in stereotactic needle biopsy of non-palpable lesions detected by mammographic screening[23,24]; Parker *et al.* reported a sensitivity of 96 per cent in a series of 102 patients[24] and found that a superior tissue sample was obtained using the 14-G rather than the 16-G or 18-G needle[23]. They concluded that this technique might be an acceptable alternative to open biopsy in women with non-palpable breast lesions. In contrast, FNAC stereotactic biopsy of non-palpable breast lesions has provided a much lower absolute sensitivity (55, 60 and 77 per cent)[25–27]

Some[2] have suggested that needle core biopsy is inappropriate for lesions of < 1 cm in size, but Baildam *et al.*[18] had positive findings with Tru-Cut in six of seven such tumours and in 33 of 35 tumours 1–2 cm in diameter (sensitivity 94 per cent).

In specialist centres, FNAC is the principal method for obtaining a non-operative tissue diagnosis of a palpable breast lump[1–5]. The technique is accurate, simple, quick to perform, cheap and virtually free of complications, and allows immediate reporting. FNAC can achieve an absolute sensitivity of 90 per cent and a false-positive rate of 0–0·6 per cent, with only 5 per cent of samples insufficient for diagnosis and 7 per cent of reports equivocal[1–5,28] In some studies the absolute sensitivity has been much lower (51–74 per cent) and the false-positive rate (0–1·6 per cent), percentage of inadequate biopsies (8–33 per cent) and percentage of equivocal reports (6–20 per cent) higher[20,29–33]. To achieve the accuracy with which FNAC is credited, all breast aspirations must be performed by an experienced aspirator[2,28], and slides interpreted by a trained and experienced breast cytologist[34]. Needle core biopsy with the Biopty gun, in contrast, requires minimal special expertise on the part of the surgeon or pathologist.

The use of needle core biopsy is complementary to FNAC. In malignant tumours it gives much more detailed information[18], for example in assessing tumour grade and distinguishing lobular, tubular and ductal carcinoma *in situ* (although only complete excision of the lesion can exclude invasive disease in the latter). Precise histology can be predicted in >90 per cent of tumours[18]. This may be of particular value in those in whom immediate surgery is not planned, e.g. elderly patients being considered for primary endocrine therapy[35] and patients being given neoadjuvant (preoperative) chemotherapy[36,37]. Needle core biopsy (with paraffin-section histology) is the only diagnostic method with a zero false-positive rate[7,9,10,15–18] The methods of FNAC and needle core biopsy should not be considered mutually exclusive Some advocate that they be used together in all lesions that are clinically or mammographically suspicious, combining their respective advantages[4,18] Needle core biopsy is of particular value when an unsatisfactory or equivocal report is obtained with FNAC.

In conclusion, for needle core biopsy of palpable breast lumps, the Biopty gun is a considerable improvement on the Tru-Cut needle; it results in a higher sampling success rate, a higher diagnostic sensitivity and a better quality of specimen when the 14-G needle is employed, and is much easier to use. The costs of the gun are not much greater than those of the Tru-Cut device (capital cost of a Biopty gun, £800; Bioptycut needles £13 *versus* Tru-Cut needles £9·50).

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Safety of fibreoptic endoscopy: analysis of cardiorespiratory events

Cardiorespiratory function during upper gastrointestinal endoscopy and colonoscopy was studied prospectively in 164 patients. Cardiorespiratory events, which were defined as oxygen saturation <90 per cent, electrocardiographic changes, heart rate <50 or >100 beats/min and systolic blood pressure <100 mmHg, occurred in 111 patients. In 24 of these, changes were attributed solely to intravenous sedation. In the remaining 140 patients, events were noted in 34 (52 per cent) of 66 upper gastrointestinal endoscopies and during 53 (72 per cent) of 74 colonoscopies. One patient suffered a myocardial infarction during colonoscopy. Although cardiorespiratory events were common (111 of 164; 68 per cent), the actual morbidity rate was low (one of 164; 0·6 per cent). Cardiorespiratory events were significantly more common in patients with a history of cardiac disease for both upper gastrointestinal endoscopy and colonoscopy (overall $\chi^2 = 7{\cdot}41$, 1 d.f., $P < 0{\cdot}05$) and more common for oesophageal dilatation than for diagnostic endoscopy ($\chi^2 = 5{\cdot}56$, 1 d.f., $P < 0{\cdot}05$). It is recommended that patients with a history of cardiac problems undergoing upper gastrointestinal endoscopy or colonoscopy and all those requiring therapeutic endoscopy should be monitored carefully to allow early detection of cardiorespiratory events, and that oxygen should be administered routinely.

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Fibreoptic endoscopy has been in widespread use for 20 years, but attention has only recently been focused on cardiorespiratory complications of the procedure[1,2]. It has been suggested that cardiorespiratory complications may be responsible for up to 50 per cent of morbidity and 60 per cent of deaths during fibreoptic upper gastrointestinal endoscopy or colonoscopy[1,3,4].

The incidence and nature of cardiorespiratory disturbances occurring during endoscopy remain contentious[1,5]. Most published series have examined one or two parameters such as pulse oximetry[4,6,7], electrocardiography (ECG)[8], or both blood pressure and pulse oximetry[9]. Studies using one parameter may not only miss important events but also fail to take account of the adverse effects of hypotension on the accuracy of pulse oximetry[10]. Where multiple monitoring methods have been used, often to examine only small numbers of selected patients[11], little consideration has been given to differentiate between the effects of sedation and the endoscopic procedure on cardiorespiratory function. To date, no prospective study has monitored continuously ECG, pulse rate, blood pressure and oxygen saturation during upper gastrointestinal endoscopy and colonoscopy or has attempted to separate the effects of sedation from those of the endoscopic procedure.

The aim of this study was to determine prospectively the prevalence and nature of cardiorespiratory changes in patients undergoing upper gastrointestinal endoscopy or colonoscopy and to identify contributory factors for untoward events

Patients and methods

Consecutive patients undergoing upper gastrointestinal endoscopy or colonoscopy in the non-specialist surgical unit of a district general hospital were studied over a 4-month period. Patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) were excluded. Before endoscopy, essential patient details and a full cardiac and respiratory history, including medications, were noted. Endoscopy was performed by one of three surgeons. one consultant, one senior registrar and one registrar. Using a compact configurable monitor (78352C; Hewlett Packard, South Queensferry, West Lothian, UK), ECG, blood pressure monitoring by a non-invasive cuff method, and digital pulse oximetry were performed with the patient in the left lateral position. These parameters were monitored continuously before administration of sedation, throughout endoscopy and for 5 min after the procedure Stable parameters before endoscopy were achieved by waiting 5 min after administering sedation

Intravenous sedation was given slowly and titrated against the level of patient sedation. For upper gastrointestinal endoscopy a median of 5 (maximum 10) mg midazolam and for colonoscopy a median of 4 (maximum 8) mg midazolam plus a median of 25 (maximum 50) mg pethidine was administered.

A Fujinon UG1-FP3 (Medical Instrumentation, Dundee, UK, external diameter 11 mm) was used for upper gastrointestinal endoscopy, and for colonoscopy a Fujinon COLII2 (external diameter 14 mm)

Significant cardiorespiratory events were defined as: heart rate <50 beats/min (bradycardia); heart rate >100 beats/min (tachycardia), systolic blood pressure <100 mmHg (hypotension), ECG rhythm or conduction disturbance or ST segment change; and oxygen saturation <90 per cent.

The technical difficulty of the procedure was graded as follows[12] grade I – complete study, minimal manipulation; grade II – complete study, moderate manipulation, grade III – complete study, extreme technical effort, and grade IV – unable to complete study owing to patient anatomy or discomfort

Cardiorespiratory events were related to preoperative cardiorespiratory history, sedation, type of procedure and the endoscopic findings.

Statistical analysis

The frequencies of events in the various groups were compared using Fisher's exact test and the χ^2 test as appropriate

Results

Gastrointestinal endoscopy was performed on 164 patients (*Table 1*): 78 aged 23–85 (mean 63) years underwent upper gastrointestinal endoscopy and 86 underwent colonoscopy (mean age 60 (range 25–82) years). In 24 patients cardiorespiratory events were noted following sedation but

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before endoscopy The remaining 140 showed no adverse response to sedation and cardiorespiratory events were recorded during 34 of 66 (52 per cent) upper gastrointestinal endoscopies and 53 of 74 (72 per cent) colonoscopies.

Cardiorespiratory events after sedation but before endoscopy

In 24 patients (15 per cent; 12 upper gastrointestinal endoscopy and 12 colonoscopy) cardiorespiratory events occurred after administration of intravenous sedation but before endoscopy (*Table 2*). A low oxygen saturation occurred in 22 patients and was associated with a heart rate <50 beats/min in three and systolic blood pressure <100 mmHg in two; two patients had a fall in systolic blood pressure to <100 mmHg alone All 24 patients received 28–40 per cent oxygen by nasal cannula or face mask after these events were noted and were excluded from further analysis.

The 12 excluded patients undergoing upper gastrointestinal endoscopy received 2–10 (median 4) mg midazolam and were aged 33–80 (mean 63) years, those who underwent colonoscopy received 2–8 (median 4) mg midazolam plus 15–50 (median 25) mg pethidine and were aged 38–82 (mean 64) years. The ages and the sedation given to the main group of 140 patients was no different from those of the 24 who exhibited drug-related effects

Cardiorespiratory events during upper gastrointestinal endoscopy

Cardiorespiratory events were recorded during 34 of 66 (52 per cent) upper gastrointestinal endoscopy procedures Additional events (*Table 3*) occurred in all ten patients who developed a low oxygen saturation: in five this was a heart rate >100 beats/min (with hypotension in two patients), ventricular ectopic beats in four (and a heart rate <50 beats/min in one of these) and ST segment depression in one patient. Overall, 15 patients developed ECG trace changes during endoscopy, most commonly ventricular ectopic beats.

Table 1 *Endoscopic procedures performed on 164 patients*

	Upper gastrointestinal endoscopy ($n = 78$)	Colonoscopy ($n = 86$)
Sex ratio (M F)	39 39	46 40
Emergencies	8	4
Therapeutic procedures		
Oesophageal dilatation	16	—
Injection of varices	2	—
Pyloric dilatation	1	—
Polypectomy	—	21

Table 2 *Effects of intravenous sedation on cardiorespiratory events*

	Upper gastrointestinal endoscopy ($n = 12$)	Colonoscopy ($n = 12$)
Oxygen saturation <90%	10	12
Systolic blood pressure <100 mmHg	4	0
Heart rate <50 beats/min	1	2
Heart rate >100 beats/min	0	0
Electrocardiographic changes	0	0

Table 3 *Effects of sedation and endoscopy on cardiorespiratory function*

	Upper gastrointestinal endoscopy ($n = 66$)	Colonoscopy ($n = 74$)
Oxygen saturation <90%	10 (15)	29 (39)
Systolic blood pressure <100 mmHg	4 (6)	23 (31)
Heart rate <50 beats/min	1 (2)	7 (9)
Heart rate >100 beats/min	19 (29)	20 (27)
Electrocardiographic changes	15 (23)	12 (16)
Ventricular ectopic beats	14	10
ST segment changes alone	1	1
Atrial fibrillation	0	1

Values in parentheses are percentages

A cardiorespiratory event was significantly more common during upper gastrointestinal endoscopy in patients with a history of cardiac disease (13 of 19 with such a history had an event compared with 21 of 47 without; $P < 0\cdot05$, Fisher's exact test) There was no association with a history of pulmonary disease.

The incidence of cardiorespiratory events was higher during therapeutic upper gastrointestinal endoscopy (13 of 18) than for diagnostic endoscopy (23 of 44). In particular, of 15 patients with oesophageal dilatation five developed an oxygen saturation of <90 per cent, all had a history of cardiac disease. Ten patients had frequent ventricular ectopic beats and one developed ST segment depression of 3 mm during the dilatation. Thus 13 of 15 patients having dilatation sustained an event compared with 23 of 44 undergoing diagnostic endoscopy ($\chi^2 = 5\cdot56$, 1 d.f., $P < 0\cdot05$) There was no relationship between the cardiorespiratory events and the amount of sedative given, the operator or the difficulty of the procedure.

Cardiorespiratory events during colonoscopy

During colonoscopy, 53 of 74 patients (72 per cent) had cardiorespiratory events. A low oxygen saturation occurred in 29 patients (*Table 3*), in 21 accompanied by further events: a heart rate >100 beats/min in eight, systolic blood pressure <100 mmHg in six, heart rate <50 beats/min in two, or some combination of these in five.

ECG changes were noted in 12 patients; in five, frequent ventricular ectopic beats occurred only when negotiating the flexures. ST segment depression occurred in three patients and in one this persisted; subsequent serial 12-lead ECG tracings and cardiac enzyme measurement confirmed myocardial infarction. Bradycardia occurred in seven patients, in one resulting in termination of the procedure

During colonoscopy 27 of the 32 patients with a cardiac history had a cardiorespiratory event compared with 26 of 42 without ($\chi^2 = 4\cdot51$, 1 d.f., $P < 0\cdot05$). There was no association between cardiorespiratory events and patient's age or respiratory history, the technical difficulty of the procedure, the amount of sedative administered or the experience of the colonoscopist.

No patient in this study experienced any mechanical complication of upper gastrointestinal endoscopy or colonoscopy. The overall cardiorespiratory morbidity rate was one in 164 patients, from myocardial infarction (one in 86 colonoscopies). There were no deaths.

Discussion

Judged by detected morbidity alone, gastrointestinal endoscopy is safe: only one of 164 patients monitored prospectively in this series suffered a serious cardiorespiratory complication. However, there is a substantial risk of patients sustaining a cardiorespiratory event These events were surprisingly common and may occur as a result of sedation or during the procedure.

Sedative effects

Despite titration of intravenous sedation to minimize haemodynamic and respiratory side-effects[7,13], it is generally held that the titration of midazolam is difficult to achieve with accuracy Some 15 per cent (24 of 164) of the present patients had cardiorespiratory events in response to intravenous midazolam with or without pethidine. The doses of benzodiazepine and opiate combined were similar to those used in other studies[4,6,7,9,11]. Opiate was not administered for upper gastrointestinal endoscopy, as is common practice in North

America. The effects of intravenous sedation usually occur within 2 min of administration[14]; this allowed separation of the effects of the sedative from those of the endoscopic procedure on cardiorespiratory function. The most common sedative effect was a fall in oxygen saturation to <90 per cent in 22 patients; this was reversed by the administration of oxygen. Such a fall in oxygen saturation has been observed in up to one-third of patients undergoing upper gastrointestinal endoscopy[15] and one-half of those having colonoscopy[4]. The rate was 15 per cent of the procedures in the present study.

Cardiorespiratory events

This study confirms the findings of previous authors. a substantial fall in oxygen saturation to <90 per cent was more common during colonoscopy (39 per cent) than during upper gastrointestinal endoscopy (15 per cent)[6,7,9,16], or than has been noted for ERCP[14]

An oxygen saturation of <90 per cent was associated with the occurrence of other cardiorespiratory events During colonoscopy, the fall in oxygen saturation may have been exaggerated in patients with a blood pressure <100 mmHg, as pulse oximetry is less accurate in hypotensive states[10,14,17,18]. The associations between low oxygen saturation and increasing age[4,6,7,12], with pain during colonoscopy, or with the duration of the procedure[6], were not confirmed Arrhythmias[3,8] and a systolic blood pressure of <100 mmHg or heart rate >100 beats/min were less common than previously suggested[8,9]. Ventricular ectopic beats, which did not persist beyond the end of the procedure[8], were noted in 23 per cent of endoscopies and 16 per cent of colonoscopies and were associated with a low oxygen saturation[19] Thus, the ectopic activity, which was confined to the period of the procedure, may relate to autonomic disturbance but was also associated with hypoxia in these patients. In one patient undergoing colonoscopy, the ST segment change persisted and later evidence confirmed that a myocardial infarction had occurred This is recognized as a rare complication of colonoscopy[8] and other gastrointestinal manipulations[20–22]

Predisposing factors

Patients with a history of cardiac or pulmonary problems (or both) may have a high incidence of cardiorespiratory events during endoscopy[9,11] related to the severity of the disease[19,23]. In the present series, patients with a cardiac history before oesophageal dilatation were particularly prone to cardiorespiratory events Overall, 90 per cent of patients with pre-existing disease developed an event during the procedure

Mechanisms

The mechanisms by which the cardiorespiratory changes occur remain speculative During upper gastrointestinal endoscopy, airway obstruction[4], gastric or salivary aspiration[7] or direct pressure on the diaphragm[24] may contribute. Before colonoscopy, bowel preparation may cause transient electrolyte shifts[12], and anxiety may trigger catecholamine release[8]. Increased vagal activity as a result of gastrointestinal manipulation may induce vasospasm, reduce coronary blood flow, and cause bronchospasm with ventilation–perfusion mismatch, hypoxia and desaturation[12,21,25,26], effects that may be potentiated by opioids and benzodiazepines[21]. The ECG changes noted may be secondary to ischaemia caused by reduced coronary perfusion, hypoxia or increased cardiac work[9].

Conclusions

The high incidence of cardiorespiratory events in this study population, even for those patients with no predisposing risk, is remarkable. Although the precise relationship between events and cardiorespiratory morbidity is not yet clear, it seems prudent to monitor essential parameters, particularly in high-risk groups[1,2].

As a consequence of this study, the authors now use pulse oximetry, ECG, blood pressure measurement, and clinical observation by a nurse trained to identify abnormalities of these parameters, on all patients undergoing colonoscopy and therapeutic endoscopy, and in any endoscopic procedure when the patient has a history of cardiac disease. As a minimum it is recommended that pulse oximetry should be used for all patients and that ECG and blood pressure monitoring should be considered for patients with known cardiac disease.

Taking an appropriate history is a cheap and useful patient screen[1,9]. Sedation may be carefully titrated for each patient and oxygen can be administered promptly[1,15,27] if saturation falls below 90 per cent Alternatively, it may be prudent to give oxygen to all patients from the start of sedation.

We suggest that non-invasive monitoring will result in safer gastrointestinal endoscopy and is practical for a busy endoscopy service.

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Announcement

European Surgical Fellowships

Since 1990 the Council of *The British Journal of Surgery* has awarded European Fellowships, each holding a value of up to £3000. Four Fellowships were awarded in 1990 and three in 1991.

In 1992 the scheme was expanded to allow surgeons working in other European countries to visit the UK. Four fellowships were awarded in that year, to Mr D. C. Mitchell (London), Mr T. H. Brown (Manchester), Dr E. M. Targarona (Barcelona) and Dr B. Nardo (Bologna).

It is Council's intention to offer European Fellowships once again in 1993. Applicants should submit details of their proposed itinerary and its anticipated costs, together with a curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK, by 1 February 1993.

D. C. Carter

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Barrett's oesophagus: effect of antireflux surgery on symptom control and development of complications

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Forty-five patients with histologically proven Barrett's columnar-lined oesophagus (CLO) were treated in one unit over a 9-year period. Patients were studied prospectively as part of a surveillance programme; all initially received standard conservative treatment including high-dose H_2-receptor antagonists. A satisfactory initial response was seen in 21 patients, but in 24 the symptoms were unchanged or progressed; 19 patients in the latter group were considered suitable for antireflux surgery and underwent fundoplication. Symptoms of heartburn or dysphagia persisted or recurred in 88 per cent of patients receiving medical treatment alone and complications developed in 38 per cent, including nine strictures and one adenocarcinoma. In patients undergoing antireflux surgery, symptoms persisted or recurred in 21 per cent and complications developed in 16 per cent ($P < 0{\cdot}01$)*. Complete regression of Barrett's CLO occurred in two patients (11 per cent) after antireflux surgery. The results of this study suggest the superiority of antireflux surgery over pharmacological acid suppression in the control of symptoms and prevention of complications in patients with Barrett's CLO.*

Barrett's columnar-lined oesophagus (CLO) has a marked propensity to develop serious complications[1]. In more than 50 per cent of patients there is an associated stricture or ulceration and tendency to haemorrhage, perforation or malignant change[2,3]. Gastro-oesophageal reflux disease (GORD) is almost invariably present in patients with Barrett's CLO but the reason why only some of those with reflux develop an abnormal glandular lining in the oesophagus, and why some of these are more prone to complications, is not known.

Patients with Barrett's CLO frequently have a severe degree of gastro-oesophageal reflux which, associated with the high frequency of complications, presents a therapeutic challenge[4]. The management of Barrett's CLO remains controversial, ranging from no treatment in the absence of symptoms to pharmacological acid suppression and antireflux surgery, but the relative merits of each form of treatment are unknown.

The aim of this study was to compare the efficacy of pharmacological acid suppression and antireflux surgery on the control of symptoms and incidence of complications in Barrett's CLO.

Patients and methods

A total of 45 patients with Barrett's CLO were treated at this hospital over a 9-year period. Patients with oesophageal carcinoma at first presentation were excluded from the study. Initial symptoms were recorded using a standard questionnaire, *Table 1* shows the grading used for symptom severity. Flexible endoscopy was performed to document the length of columnarization above the gastro-oesophageal junction and to identify the presence of stricture or other complication. Only patients with a circumferential columnar lining >3·0 cm above the endoscopically determined gastro-oesophageal junction were diagnosed as having Barrett's CLO. The nature of the glandular epithelium was confirmed by biopsy. Strictures were dilated before starting therapy, using Celestin dilators passed over a guidewire. Full dilatation to 56 Fr was achieved in all patients.

Twenty-nine patients underwent oesophageal manometry and 24-h ambulatory simultaneous oesophageal and gastric pH monitoring as described previously[5]. A defective lower oesophageal sphincter (LOS) was defined as one with pressure <6 mmHg, abdominal length <1·0 cm, or overall length <2·0 cm, as described by DeMeester and colleagues[6,7]. Weak lower oesophageal peristalsis was defined as peristaltic amplitude below the 10th percentile of normal subjects[8].

Table 1 *Grading for the assessment of heartburn, regurgitation, dysphagia and epigastric pain*

	Frequency of symptoms			
Score	Heartburn	Regurgitation	Dysphagia	Epigastric pain
1	Monthly	Monthly	Occasional	Monthly
2	Weekly	Weekly	Solids only	Weekly
3	Daily	Daily	Semisolids	Daily
4	—	—	Liquids	—

Each patient was treated for a period of 3–6 months with high-dose H_2-receptor antagonist therapy (ranitidine 600 mg daily), and Gaviscon (Reckitt and Coleman, Hull, UK), 10 ml 6-hourly in addition to standard general measures. The initial dose of ranitidine in 37 of the 45 patients was 600 mg, in eight a daily dose of 300 mg was used initially but was increased to 600 mg after 6–12 weeks. The latter group was then reassessed after 3 months. All patients thus completed at least 3 months of maximum medical therapy, compliance was checked by returned tablet count during this period. A symptomatic assessment was made after the initial trial of medical therapy and patients with residual reflux symptoms, or dysphagia from persistent or recurrent stricture, were offered antireflux surgery. Of the 45 patients who started therapy, 21 had an initially good response to medical treatment at 3 months and continued to take high doses of ranitidine. Five of the remaining 24 patients were considered ineligible on the basis of age and general condition, but 19 underwent antireflux surgery, which comprised restoration of the LOS to the abdominal cavity, accentuation of the flap-valve mechanism of the cardia, and partial anterior fundoplication as previously described[9,10].

Endoscopy was performed annually, and additional endoscopic examination carried out if clinically indicated. Symptoms of heartburn,

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Table 2 *Patient details*

	Medical treatment ($n = 26$)	Surgical treatment ($n = 19$)
Age (years)*	70 (40–91)	62 (26–74)
Sex ratio (M:F)	12:14	11:8
Length of Barrett's mucosa (cm)*	5·0 (3–10)	6·0 (3–11)
Duration of follow-up (years)*	3·0 (1–9)	3·0 (1·5–9)

*Values are median (range)

regurgitation, dysphagia and epigastric pain were recorded and graded using the standard questionnaire at each visit. The number of recurrent strictures was recorded as the number of patients requiring dilatation during the course of the study. In addition, the number of dilatations required for each patient was recorded

The age and sex ratio of the two groups is shown in *Table 2* The extent of the lower oesophagus covered by circumferential glandular epithelium is also shown and was similar in each set of patients. Follow-up was for a median of 3 years in each group.

Statistical analysis

Symptoms were assessed annually and the median score for each symptom in each patient recorded Symptoms before and after treatment in the two groups were compared using the Wilcoxon signed rank test. Intergroup comparisons of symptoms were made using the Wilcoxon rank sum test. The proportion of patients with persistent or absent symptoms and the incidence of complications were compared using Fisher's exact test. $P < 0{\cdot}05$ was considered significant.

Results

Manometry and oesophageal pH monitoring before treatment showed that patients treated medically or surgically had similar severe degrees of GORD. Oesophageal manometry (*Table 3*) showed a defective LOS in the majority of patients, with a mean LOS pressure of 4 mmHg. The peristaltic amplitude of oesophageal body contractions measured in 29 patients was abnormally weak in 14 and, although there was a predominance of these in the medically treated group, this was not significant (*Table 3*). Ambulatory 24-h pH monitoring indicated that both groups had a severe degree of acid reflux and an abnormally high exposure to pH >7 (*Table 4*). There was no significant difference in the pretreatment acid pH profile of the medically and surgically treated patients, but there was a greater exposure to pH >7 in the surgically treated group before surgery.

Symptoms before treatment were also similar in both groups, with heartburn and dysphagia being the most troublesome (*Table 5*). Both of these symptoms improved more after surgery than after medical therapy. Symptoms of heartburn (grade 2 or higher) and/or dysphagia (grade 1 or higher) persisted or recurred in 23 patients (88 per cent) on medical treatment and in four (21 per cent) after antireflux surgery ($P < 0{\cdot}01$). Complications developed in ten patients (38 per cent) after medical therapy, and included stricture in nine and carcinoma in one. After antireflux surgery three patients (16 per cent) developed complications: stricture in two and carcinoma in one ($P < 0{\cdot}05$). The mean extent of the Barrett's mucosa was unchanged in each group, although after surgery columnarization regressed completely in two patients (from 7 and 4 cm).

Table 3 *Manometric assessment of the oesophageal body and lower oesophageal sphincter before therapy*

	Medical treatment ($n = 16$)	Surgical treatment ($n = 13$)
Defective lower oesophageal sphincter	10	11
Weak oesophageal peristalsis	9	5

Differences between groups were not significant (Fisher's exact test)

Table 4 *pH profile before therapy*

	Medical treatment ($n = 16$)	Surgical treatment ($n = 13$)
Percentage of time at pH < 4	14 (1–49)	15 (3–68)
DeMeester[8] composite score at pH < 4	41 (2–139)	43 (8–182)
Percentage of time at pH > 7	8 (0–59)	16 (0–47)*

Values are median (range) *$P < 0{\cdot}05$ (Wilcoxon rank sum test)

Table 5 *Symptom scores before and after therapy*

	Medical treatment		Surgical treatment	
	Before	After	Before	After
Heartburn	2 (2–3)	2 (0–3)	3 (2–3)	0 (0–2)*
Regurgitation	1 (0–2)	0 (0–2)	1 (0–3)	0 (0–0)
Dysphagia	2 (0–4)	1 (0–4)	2 (0–4)	0 (0–2)*
Epigastric pain	1 (0–3)	0 (0–3)	1 (0–3)	0 (0–3)

Values are median (range). *$P < 0{\cdot}05$ (before *versus* after surgery, Wilcoxon signed rank test)

Nine strictures required intervention in medically treated patients; the mean number of dilatations required for each stricture was four. In the surgically treated group one patient needed one dilatation, and one required six dilatations. In both of these cases the strictures represented recurrences of previous stricture, while in the medical group recurrence occurred in six patients and a new stricture developed in three.

Discussion

While there is general agreement concerning the need for surveillance of patients with Barrett's CLO[11,12], it is surprising that no clear guidelines exist regarding the treatment of these patients, or indeed whether they should be treated at all in the absence of significant symptoms[13]. Where treatment is recommended, both pharmacological acid suppression and antireflux surgery have been recommended[11,14,15], but no study has examined the relative merits of these approaches. Although not randomized, this study was performed prospectively as part of an ongoing surveillance programme and reflects the current clinical management of patients with Barrett's CLO at this unit

The results of preoperative manometry showed similar loss of LOS function and oesophageal body motility before treatment in both medically and surgically treated patients. The pH profile in the two groups showed similar exposure to pH <4 but the surgical patients had greater exposure to pH >7. These patients had not responded to medical therapy in the first 3 months, a failure that may have been related to this alkaline exposure. Both groups contained a significant number of patients with increased alkaline exposure and a high incidence of abdominal pain suggesting gastritis. It is interesting to note that neither medical nor surgical therapy had a significant effect on the symptom scores for abdominal pain, as might be expected if the abdominal symptoms were related to alkaline exposure.

The results of this study show that the symptomatic response in patients treated medically was poor and the rate of stricture recurrence and formation high, in contrast to the good symptomatic response and low rate of stricture recurrence after surgery. No new stricture occurred after antireflux surgery.

The results of medical therapy in this study are similar to those of Atkinson and Robertson[15], who compared stricture recurrence in patients with and without Barrett's oesophagus. However, these authors found that conservative measures were less successful in non-Barrett's strictures than in Barrett's oesophagus and, based on this, concluded that columnar epithelialization was not in itself an indication for antireflux surgery. In contrast, this study has compared medical and surgical therapy directly and found the latter to be preferable in Barrett's oesophagus. The results of antireflux surgery in the prevention of stricture recurrence are similar to those of a randomized study between medical and surgical management of strictures previously reported from this unit[16,17].

This study has not shown any overall reduction in the length of Barrett's epithelium with either treatment but, as in previous reports[18], there were two cases of complete regression of Barrett's epithelium in surgical patients. There was no difference in the rate of malignant change, as one patient from each group subsequently developed cancer. Although only a small number of patients was studied, this represents a relatively high rate of malignant change (1 in 90 patient-years), comparable to findings from other series with prospective endoscopic follow-up (Robertson *et al.*[12], 1 in 56 patient-years; Hameeteman *et al.*[19], 1 in 52 patient-years). The occurrence of malignant change in both groups encourages vigilance in the follow-up of patients with Barrett's CLO regardless of the method of treatment. The reason for malignant change in Barrett's oesophagus is not understood but it may be consequent on continued gastro-oesophageal reflux[6,20]

The number of patients followed after surgical therapy reported in the world literature is still small and no conclusion can be inferred on whether the abolition of reflux by successful antireflux surgery confers any benefit in preventing malignant change. One of the difficulties with this form of prophylactic therapy is that the carcinogenic stimulus may have been present for some years before treatment is started. The process of malignant transformation may have already begun and a latent period may elapse before it manifests as frank carcinoma. Animal studies indicate a cocarcinogenic effect of duodenal but not of gastric juice in the rat oesophagus[20]. Whether duodenal juices play a role in the development of carcinoma in the human oesophagus is not known.

This study does not indicate why medical therapy failed in over one-half of the patients treated. Since medication was aimed at acid suppression the implication is that either the degree of suppression was insufficient or the presence of non-acid injurious agents in the refluxed material continued unabated, and indeed may have been enhanced by the neutralizing effect of acid. From studies[4,21] that show abnormal episodes of alkalinization in gastric and oesophageal pH and the coexistence of gastritis and raised serum gastrin levels in patients who have complications associated with Barrett's oesophagus[4], we believe that duodenogastric reflux may play a role in the development of complications in Barrett's CLO. Successful antireflux surgery creates a mechanical barrier to refluxed material regardless of composition, and the greater efficacy of such surgery over pharmacological acid suppression supports the hypothesis that components of the refluxate other than acid or pepsin may play a role in the development of complications.

Inadequate acid suppression is another possible explanation for the high incidence of failure of treatment, but in this study a high dose of H_2-receptor antagonist was administered. A recently published prospective randomized trial of medical and surgical therapy in GORD reported a similar rate of failure of acid suppression therapy to relieve symptoms[22]. In other recent studies even greater degrees of acid suppression using the new proton pump inhibitor omeprazole have still been associated[23–25] with a significant failure rate in healing oesophagitis within the first 8 weeks, which approaches 50 per cent in the most severe grades of oesophagitis. While some Barrett's ulcers have been healed by high-dose omeprazole therapy, regression of Barrett's CLO has been reported only rarely[26–28]

As Barrett's CLO represents the extreme end of the spectrum of GORD, with a high incidence of failure of the LOS, oesophageal pump failure and consequently high levels of oesophageal acid exposure, it is perhaps not surprising that conventional antireflux medication should be less successful than in uncomplicated erosive oesophagitis[29] Furthermore, the association between increased oesophageal alkaline exposure and complications of Barrett's CLO[21] suggests that acid suppression would be less effective in preventing and treating complications. The finding in the present study that there was a greater exposure to pH >7 in the surgically treated patients before surgery may be explained by the fact that these were selected because of early failure of acid suppression. Their subsequent good response to surgery may have been related to the reduction of all types of refluxed material, both acid and non-acid.

Some patients with Barrett's CLO are elderly and not all are suitable for antireflux surgery. In the present study, antireflux surgery was deemed inappropriate in 21 per cent of patients in whom medical treatment failed. However, in the remainder it was well tolerated and performed with a minimal morbidity rate and no deaths.

The results of this prospective non-randomized study strongly suggest that antireflux surgery is more effective than pharmacological acid suppression in the control of symptoms and prevention of complications in patients with Barrett's CLO. We believe these results justify the conduct of a randomized prospective trial in patients eligible for either treatment.

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Symptom index as a marker of gastro-oesophageal reflux disease

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Forty per cent of patients with heartburn may have no evidence of oesophagitis or of abnormal oesophageal acid exposure. The symptom index correlates symptoms that occur during pH monitoring with episodes of acid reflux, being the number of symptoms during reflux divided by the total number occurring during monitoring. This index was assessed in 61 patients with heartburn. In 39 patients with endoscopic evidence of oesophagitis or abnormal acid exposure times on pH monitoring, the symptom index had a sensitivity of 90 per cent. Of the 22 patients with no objective abnormality, the index was ≥50 per cent in five (23 per cent) whose symptoms were presumably due to acid reflux despite results of other investigations being normal, suggesting an acid-sensitive oesophagus. The symptom index is a useful additional measure in the investigation of patients with suspected gastro-oesophageal reflux disease.

Fifty per cent of patients investigated for gastro-oesophageal reflux disease (GORD) have a normal result from upper gastrointestinal endoscopy[1]. One-fifth of such patients have increased acid reflux demonstrated by ambulatory oesophageal pH monitoring[2]. Forty per cent of patients with significant dyspepsia have no demonstrable abnormality.

The 'symptom index' is described as a marker of GORD to distinguish patients whose symptoms are related to episodes of acid reflux[3]. The index is defined as the number of symptoms occurring during reflux episodes divided by the total number of symptoms experienced during ambulatory pH monitoring. The coincidence of one of every two symptoms with acid reflux (symptom index of 50 per cent) and correlation of one symptom in four (index of 25 per cent) have both been recommended to define GORD[4,5]

The aims of this study were to assess the sensitivity of these 25 and 50 per cent symptom index values in diagnosing GORD in patients with proven disease (positive endoscopy and/or pH monitoring) and to compare the results with those from patients whose tests were normal.

Patients and methods

Seventy-two consecutive patients attending with frequent heartburn warranting endoscopy were recruited. Patients were excluded if they had previously been investigated for dyspepsia or had taken H_2-receptor antagonists, omeprazole or regular non-steroidal anti-inflammatory drugs within 2 weeks of endoscopy.

Ambulatory oesophageal pH monitoring was performed for 20 h in each patient. A monocrystalline antimony electrode (Synectics Medical, Oxford, UK) was calibrated in buffers of pH 7·01 and 1·07 and placed 5 cm above the manometrically determined upper border of the lower oesophageal sphincter. This electrode and a silver chloride skin electrode were connected to a digitrapper (Synectics Medical). Patients documented their symptoms in a diary card and pressed an event marker on the digitrapper to record the exact time of symptom perception related to the pH trace.

Data were analysed using the Esophogram program (Gastrosoft, Milwaukee, Wisconsin, USA). More than 4·7 per cent of the total monitoring time at pH <4 was taken as abnormal. This value is the 95th percentile of an age- and sex-matched group of 20 healthy volunteers (unpublished results). A reflux episode began at pH <4 and ended when the pH rose above this value. A symptom was designated reflux-related if it occurred during or within 2 min of a reflux episode. The symptom index was calculated for each patient.

Patients were divided into those with proven GORD (positive results of endoscopy and/or pH monitoring) and those with no objective abnormality. The frequency of a positive symptom index was compared between the two groups using the χ^2 test with Yates' correction.

Results

At endoscopy, 27 patients had oesophagitis and 34 had no abnormality; 11 had gastric or duodenal pathology and were excluded. Ambulatory pH monitoring demonstrated increased acid reflux in 12 of the 34 patients with normal endoscopic findings. In 22 patients both investigations were negative and in 39 at least one test was positive (*Table 1*).

In the group with GORD the symptom index was highly positive (≥50 per cent) or low (<25 per cent) (*Figure 1*): none had an intermediate result (25 per cent ≤ symptom index <50 per cent). Both suggested symptom index thresholds (25 and 50 per cent) yielded the same sensitivity for proven GORD (35 of 39; 90 per cent).

Over half the patients with no objective abnormality (13 of 22) had a low symptom index (*Figure 1*). In five patients the index was ≥50 per cent and in four lay between 25 and 50 per cent. The 25 per cent symptom index was therefore positive in nine of 22 patients (41 per cent). This figure dropped to five of 22 (23 per cent) when the 50 per cent symptom index was adopted.

Compared with the group with normal investigations, significantly more patients with proven GORD had a positive symptom index when either 25 or 50 per cent thresholds were used ($P < 0{\cdot}001$).

Discussion

This study demonstrates that the symptom index is a sensitive measure of GORD, being positive in 90 per cent of patients with proven reflux whether the 50 or 25 per cent value is adopted. These results are similar to those of Hewson *et al.*[5], who used the 25 per cent threshold.

Using either value, significantly more patients with proven GORD had a positive result compared with those with no objective abnormality. This is as expected since the latter group may contain patients whose symptoms have a cardiac or oesophageal dysmotility cause. It is in this group that the symptom index may be of greatest diagnostic value. Its ability to define acid reflux as the cause of pain avoids further investigation, helps reassure the patient and directs appropriate treatment.

The choice between a 50 and 25 per cent threshold is important. The possible bimodal distribution in patients with reflux (*Figure 1*) suggests that all those with a symptom index ≥50 per cent can be diagnosed as having acid-related symptoms. Using this definition, five patients have been identified whose symptoms are caused by GORD but in whom

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Table 1 *Results of pH monitoring and symptom index calculation for different groups*

Patients	Percentage of total time at pH <4*	No of symptoms during test*	No. of patients with symptom index ⩾50%†	No. of patients with symptom index ⩾25%†
Oesophagitis with reflux ($n = 22$)	11·4 (5·9–48·7)	4 (1–24)	20 } 35 (90)	20 } 35 (90)
Oesophagitis without reflux ($n = 5$)	4·1 (3·3–4·6)	5 (2–10)	5	5
Reflux alone ($n = 12$)	9·0 (5·5–28·5)	5 (1–14)	10	10
No objective abnormality ($n = 22$)	1·7 (0·2–4·0)	2 (1–13)	5 (23)	9 (41)

*Values are median (range), †values in parentheses are percentages. Oesophagitis is defined endoscopically and acid reflux by pH monitoring

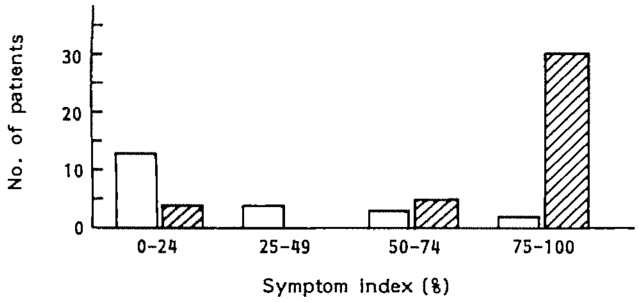

Figure 1 *Distribution of symptom index in patients with normal investigations* (□) *and those with proven oesophagitis and/or acid reflux* (■)

there was no other objective evidence of abnormal reflux. These patients can be managed appropriately with acid suppression.

That acid is the cause of the pain in patients with no objective abnormality and symptom index between 25 and 50 per cent is less clear. In these patients two further steps are recommended before other investigations such as oesophageal manometry or cardiac treadmill are carried out. Oesophageal pH monitoring should be repeated and the patients should be given a trial of acid suppression. Up to 25 per cent of those with reflux symptoms may have a normal result one day and abnormal levels of acid reflux subsequently[6,7]. This study demonstrates the benefits of a symptom index in patients with typical heartburn. Its results must be interpreted with caution when dealing with those with symptoms such as atypical chest pain.

The symptom index is a sensitive measurement of reflux and is of greatest use in patients who have normal results from endoscopy and pH monitoring. In these patients a symptom index ⩾50 per cent allows the diagnosis of GORD and prescription of appropriate treatment.

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Ambulatory measurement of oesophageal function: clinical use of a new pH and motility recording system

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Conventional oesophageal manometric studies are open to criticism in that they take place on fasted immobile subjects in the artificial setting of a motility laboratory. A new 24-h pH and motility recording system combined with computerized data analysis was used to study patients with gastro-oesophageal reflux disease and oesophageal motor abnormalities under ambulant conditions. Acid reflux episodes were found to be precipitated by a variety of events with recognizable pressure patterns. Acid clearance abnormalities were demonstrated in patients with erosive oesophagitis but were confined to those with abnormal oesophageal motor function. Improved diagnostic accuracy was demonstrated in the recognition of oesophageal motor disorders.

Oesophageal manometry has established[1] the existence of a lower oesophageal sphincter (LOS) and described its behaviour before and during acid reflux episodes[2]. A normal range of LOS pressures[3] and a range of oesophageal body motor functions have been described[4]. Conventional station pull-through manometry has allowed classification of various oesophageal motor abnormalities based on normal control data[5], in conjunction with other diagnostic tests[6].

Such oesophageal manometric measurements are, however, open to criticism They mainly involve the use of water-perfused measuring equipment. As pressure transducers lie outside the body, they must be levelled with the outlet port of the perfusion catheter in the oesophagus. Consequently, studies take place on supine starved subjects who must remain immobile. The standard test involves pulling the manometry catheter across the LOS to establish LOS pressure, and then asking the patient to swallow a small quantity of water ten times, with a 30-s interval between each swallow, to assess oesophageal body motility. As it is rare for patients to experience their usual symptoms or to get acid reflux during these studies, various provocative manoeuvres have been employed (abdominal compression, straight leg raising[7], gastric distension with carbon dioxide[8] or balloons[9], pharmacological stimulation with edrophonium or hydrochloric acid[10]). The results from these unphysiological hospital-based short-term studies may be quite different to measurements obtained during normal daily activities.

Ambulatory studies that combine measurement of pH and motility have been reported over the past 5 years but are still few in number[11–17]. Most have technical limitations such as insufficient memory capacity in the recording box, manual data analysis of selected parts of the recording, or transducer locations only in the oesophageal body. In the present study a unique system has been developed that incorporates oesophageal pH measurement and simultaneous oesophageal body, LOS and intragastric pressure recordings combined with computerized waveform analysis.

Patients and methods

pH and pressure catheters

Recordings were obtained using two connected catheters, one for pH and the other measuring pressures at multiple sites The pH catheter carried a standard antimony pH probe (Synectics Medical, Oxford, UK) located 5 cm above the manometrically determined LOS.

The 2 4-mm manometry catheter had five solid-state intraluminal pressure transducers sheathed in flexible silicone rubber (CTO-5/Sphinctometer, Gaeltec, Isle of Skye, UK) Three of these transducers were located in the oesophageal body (5 cm apart and radially offset by 120°), the lowest level with the pH probe. A fourth transducer (starting 5 cm below the lowest oesophageal body transducer) consisted of the 'sphinctometer'; its design and performance has been described in detail elsewhere[18] Essentially it consisted of a 6·3-cm long oil-filled Silastic (Dow Corning, Reading, UK) chamber connected to a strain gauge that recorded an integrated output of the pressure and length components of LOS function. Its length allowed up-and-down movement of the LOS while still retaining sphincter contact The fifth transducer lay 5 cm below the sphinctometer and was positioned in the stomach.

24-h recording unit

The recording unit (7-MPR; Gaeltec) was carried by a shoulder strap and weighed 850 g when loaded with four AA size alkaline batteries There were three buttons two for controlling the unit and one for use as an event marker during the study The system, using multiple transducers is able to produce 24-h recordings because the unit processes the incoming pressure signals so that all rapidly changing pressure data are retained while few data points are stored when little pressure activity is occurring (i.e during sleep) This data compression (validated by comparison with a manual analysis of the same recording periods in ten subjects) allows a full patient record to be stored on one 0·79-megabyte floppy disc

Data were offloaded to a 410/1 Acorn Archimedes computer (32-bit, 4-megabyte RAM, Acorn Computers, Cambridge, UK) The automated analysis program scanned the patient recording for pressure rises >20 mmHg above the baseline for each pressure transducer. Swallow waves were classified as peristaltic (when contractions recorded in the oesophageal body showed a continuous progression down the oesophagus in all three transducers), non-propagated (if a distal oesophageal contraction failed to follow a propagated wave from the proximal two transducers), simultaneous (contractions in all three transducers at the same time) and segmental (isolated contractions in any of the three oesophageal transducers) All other patterns of contraction were grouped as complex. A table of the different types of waves and parameters describing these (e g wave amplitude, velocity and duration) was generated by the computer.

The oesophageal pH channel was scanned to identify and record pH fluctuations A reflux episode began when the pH fell below 4·0 and ended when it rose above 5·0

Patients

In this series 141 patients and 18 asymptomatic control subjects were studied Referrals included non-obstructive dysphagia, atypical chest pain and gastro-oesophageal reflux symptoms. Before the pH and

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motility study patients underwent upper gastrointestinal endoscopy or barium assessment and, where indicated, exercise electrocardiography or coronary angiography All medication known to affect gastric pH or oesophageal motility was stopped for at least 48 h before the pH and motility study The pH and pressure catheters were calibrated, tied together and passed through the anaesthetized nose (1 per cent lignocaine spray) into the stomach A standard motility test was carried out, with the patient in a sitting position, by slowly withdrawing the catheter in 1-cm increments to establish the position and resting pressure of the LOS Catheters were then secured so that the pH probe and lowest oesophageal pressure transducer were 5 cm above the LOS. A series of ten wet swallows were then carried out using 4-ml aliquots of water, at room temperature, administered through a syringe at 30-s intervals For the 24-h study, patients were instructed to carry out normal daily activities and record meals, drinks, position, activities and symptoms on a diary sheet and by use of the event button. After completion of the recording, data were offloaded to the computer for automated analysis

Controls

Oesophageal function was assessed in 18 control subjects (group 1) (12 men, six women, median age 52 (range 19–73) years) for eating, interdigestive and nocturnal periods. Contraction waves were classified as described and the amplitude, duration and velocity of peristaltic waves recorded. The frequency of the different oesophageal contractions was noted. These data and pH recordings served as a baseline for comparison with patient groups.

Mechanisms of gastro-oesophageal reflux

Various events such as coughing, sniffing, belching and straining produced recognizable pressure patterns on the manometry tracings (*Figure 1*). It was noted that acid reflux episodes often followed such pressure changes. Consequently, reflux episodes occurring during normal daily activities were studied in controls (group 1) and two patient groups. The findings were correlated with manometric events. LOS behaviour at the moment of acid reflux was assessed Ten patients with gastro-oesophageal reflux disease (GORD) but no endoscopic oesophagitis (group 2) and ten patients with erosive oesophagitis (group 3) (Savary–Miller[19] grades 2 and 3) were studied. Reflux episodes were classified as: spontaneous if no pressure activity preceded the pH fall; belch related, stress induced (coughing, sneezing, sniffing, straining, hiccuping); motor related if preceded in the 15 s before a pH fall by an oesophageal body contraction (peristaltic or otherwise), or unclear if two or more of the above occurred so that the precipitating cause of the reflux episode could not be confidently determined (*Figure 1*).

Oesophageal acid clearance

The following parameters were studied for each acid reflux episode in 14 control subjects and in 14 age- and sex-matched patients with erosive oesophagitis· duration of the reflux episode, time to the first peristaltic contraction, time between peristaltic contractions, and the proportion of the different types of oesophageal contractions occurring during the reflux episode.

Oesophageal motor disorders

Oesophageal motor disorders were diagnosed by station pull-through manometry using established criteria[5]. The diagnosis of motor disorders by 24-h manometry is not clearly established. Achalasia was defined as the complete absence of oesophageal body peristalsis over the whole study period combined with a non-relaxing LOS Diffuse oesophageal spasm was defined by the presence of oesophageal body contractions with durations > 15 s combined with multiple peaks (whose amplitudes were often > 180 mmHg) and the presence of such contractions at the time of symptoms. As simultaneous contractions can occur with a frequency of up to 40 per cent in normal subjects when studied over prolonged periods[17], standard motility criteria are inappropriate for the diagnosis of diffuse oesophageal spasm in 24-h studies Nutcracker oesophagus was defined as oesophageal body peristaltic waves with mean amplitudes during eating of > 180 mmHg and during the interdigestive period of > 120 mmHg (based on the 95 per cent range of normal control data). Other oesophageal motor patterns outside the 95 per cent range of normal values for the same recording period (meals, interdigestive and sleeping) were classified as non-specific oesophageal motor disorders

Statistical methods

A normal range of pressure values was established using parametric tests Data from studies comparing patient groups were assumed not to be normally distributed and were expressed as median (interquartile range (i.q.r)). The Wilcoxon rank sum and signed rank tests were employed as appropriate.

Results

A total of 159 studies were carried out, including 18 on control subjects The presence of the combined pH and motility catheters and the correlation with symptoms showed that 86 patients had symptomatic GORD, 26 had oesophageal motor disorders, and in 29 the oesophagus was excluded as a cause of symptoms.

Control subjects

The median recording length was 21·2 (i.q.r 20·2–22·1) h. The control subjects experienced a median of 8 (i.q.r. 5–18) reflux episodes per patient, and a median time at pH < 4 of 0·9 (i.q.r 0·2–1·7) per cent. Altogether, 181 reflux episodes were observed in control subjects; the LOS demonstrated relaxation before the pH fall in 62 per cent. In the other 38 per cent of reflux episodes no relaxation could be observed because LOS pressure was already low, common cavity pressure activity obscured LOS behaviour, or device malfunction occurred. The median (i.q.r.) peristaltic wave frequency was significantly greater during eating (120 (88–150) waves per h) than during the interdigestive (23 (20–37) waves per h) and the night-time (9 (6–13) waves per h) periods (*Figure 2*). Median (i.q.r) distal peristaltic wave amplitude (67 (39–79) mmHg) was greater and wave velocity (30 (27–33) mm s^{-1}) lower during eating compared with interdigestive and night-time periods (*Figure 2*). There were no contractions of duration > 15 s combined with multiple peaks of amplitude > 180 mmHg.

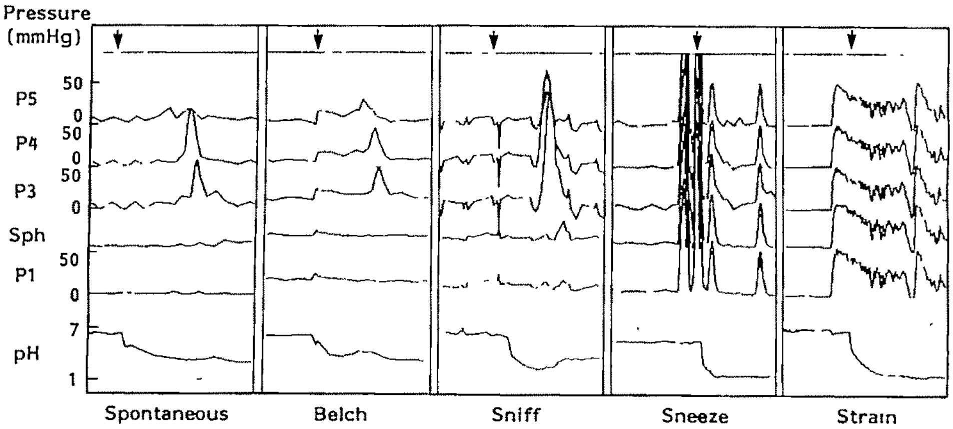

Figure 1 *Characteristic pressure patterns related to acid reflux episodes (arrows) P3–P5, oesophageal pressure transducers, Sph, sphinctometer, P1, gastric pressure transducer*

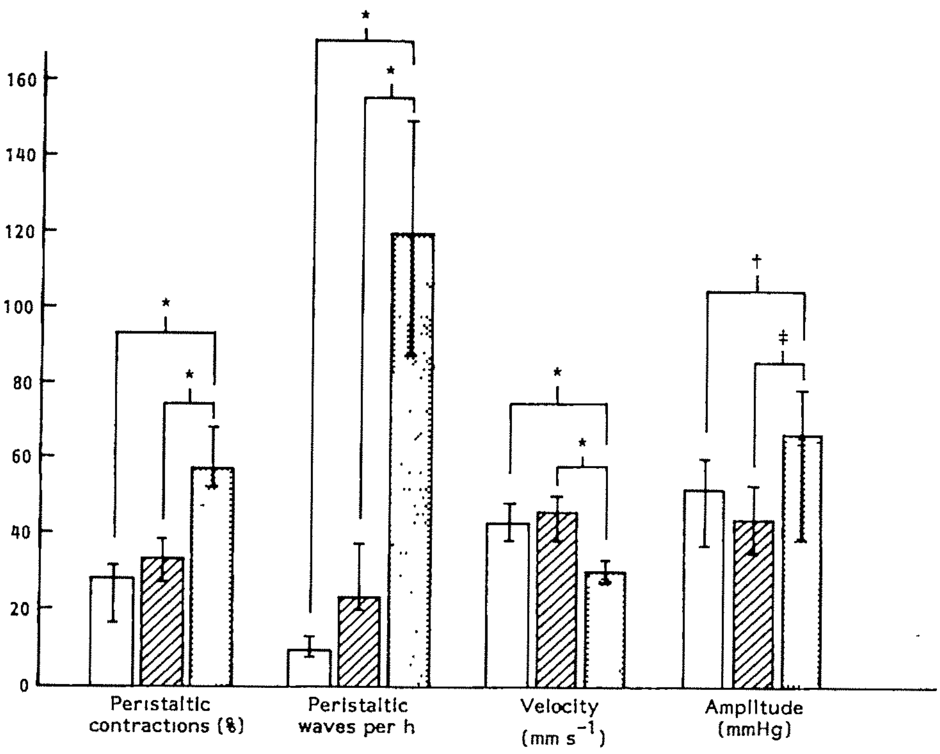

Figure 2 *Peristaltic wave data over 24 h in control subjects. Values are median (interquartile range). Periods are* □, *nocturnal;* ■, *interdigestive;* □, *eating.* *P < 0·001; †P < 0·02, ‡P < 0·002 (*Wilcoxon signed rank test*)

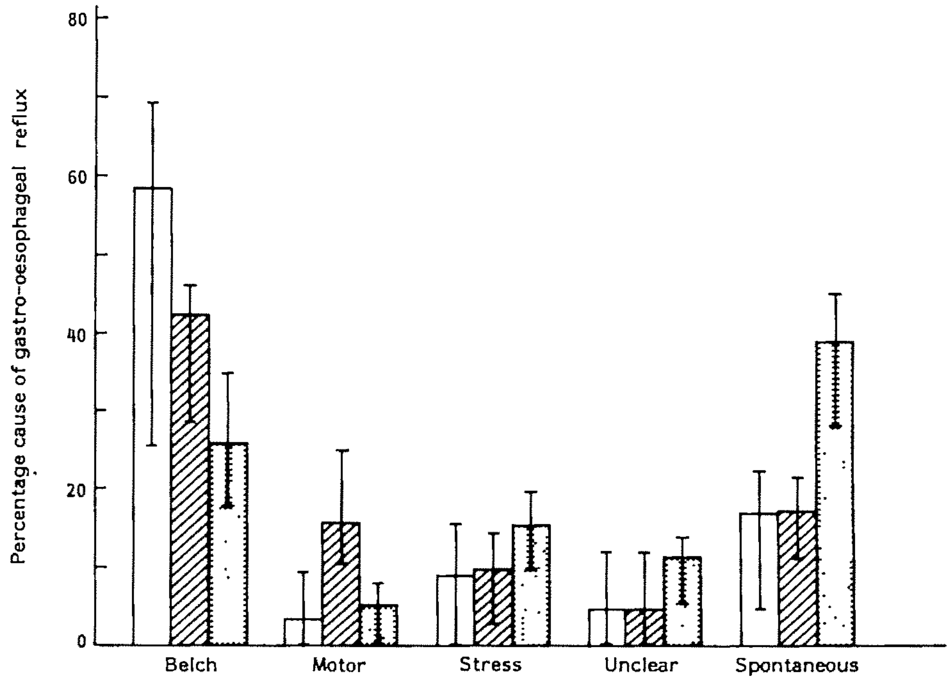

Figure 3 *Different causes of acid reflux episodes. Values are median (interquartile range) percentage of total number of gastro-oesophageal reflux episodes in each group.* □, *Control,* ■, *gastro-oesophageal reflux with no oesophagitis,* □, *gastro-oesophageal reflux with oesophagitis*

Mechanisms of gastro-oesophageal reflux

Controls had fewer reflux episodes (median 8 (i.q.r. 5–18)) than patients with reflux but no oesophagitis (median 41 (i.q.r. 23–51)) and patients with erosive oesophagitis (median 71 (i.q.r. 42–90), $P < 0{\cdot}01$). The median number of reflux episodes in control subjects was only eight, and belching was found to be the precipitating cause in 59 per cent of them (*Figure 3*). This was significantly greater than the 26 per cent in patients from group 3 ($P < 0{\cdot}05$). In contrast, spontaneously occurring reflux through a low-pressure LOS was the main cause of acid reflux in the patients with erosive oesophagitis (group 3) ($P < 0{\cdot}001$ *versus* groups 1 and 2) though even in this group belching caused 26 per cent of episodes.

Acid clearance

Control subjects had significantly fewer reflux episodes and these were of shorter duration than in patients with erosive oesophagitis. The median (i.q.r.) time to the first peristaltic contraction was significantly shorter in group 1 than in group 3 (45 (21–64) *versus* 87 (55–119) s, $P < 0\cdot05$), as was the interval between peristaltic contractions (65 (46–92) *versus* 125 (99–162) s, $P < 0\cdot01$). When patients were divided into those with normal or abnormal 24-h oesophageal body motor function based on criteria derived from the control subjects, there was no difference in the median (i.q.r.) time to the first peristaltic contraction (45 (21–64) *versus* 63 (37–75) s, P not significant), the time between peristaltic contractions (65 (46–92) *versus* 99 (56–110) s, P not significant) and the proportion of contractions during the acid reflux episode that were peristaltic (63 (52–72) *versus* 73 (65–78) per cent, P not significant) between control subjects and patients with oesophagitis but normal oesophageal body motility. There were significantly longer median (i.q.r.) times to the first peristaltic contraction (45 (21–64) *versus* 132 (89–191) s, $P < 0\cdot01$), to the time between peristaltic contractions (65 (46–92) *versus* 170 (123–230) s, $P < 0\cdot001$) and for the percentage of peristaltic waves that occurred during the reflux episode (63 (52–72) *versus* 49 (35–50) per cent, $P < 0\cdot01$) between controls and patients with oesophagitis and abnormal oesophageal body motility.

Oesophageal motor disorders

Table 1 shows the distribution of different oesophageal motor abnormalities detected by conventional station pull-through and by 24-h oesophageal manometry. Ten patients who were classified as normal on station pull-through manometry were found to have abnormalities on 24-h manometry: four had diffuse oesophageal spasm and six had non-specific motor abnormalities. *Figure 4* shows a normal conventional oesophageal study in a patient with nocturnal chest pain whose 24-h study showed typical contraction waves of diffuse oesophageal spasm at night. Two further patients had their station pull-through manometry diagnosis changed following the 24-h study, one from non-specific oesophageal motor disorder to diffuse oesophageal spasm and one from nutcracker oesophagus to diffuse oesophageal spasm.

Table 1 *Oesophageal motor abnormalities diagnosed by station pull-through compared with 24-h manometry*

Motor disorder	Station pull-through manometry	24-h manometry
Achalasia	7	7
Diffuse oesophageal spasm	1	7
Nutcracker oesophagus	2	1
Non-specific	6	11
None	10	0
Total	26	26

Discussion

Like early hospital-based pH studies, conventional oesophageal manometry can be criticized as being unphysiological. Previous experiments examining the motor events around acid reflux episodes have used the water-perfused Dent sleeve. Transient inappropriate relaxations of the LOS have been found to be the cause of most reflux episodes in control subjects[2] and patients with GORD[20]. Normal subjects, however, do not spend most of the day lying supine. In this study the combined pressure transducers in the oesophageal body and stomach have revealed that most reflux episodes in control subjects are caused by belching. This explains why postprandial reflux is common. Belching on a stomach full of recently swallowed food and air allows the inadvertent reflux of gastric acid. This event was found to be regularly associated with reflux in all patient groups. In patients with erosive oesophagitis, spontaneously occurring acid reflux through a low-pressure sphincter was found to predominate. It was not possible to draw valid conclusions about transient LOS relaxations in an ambulant situation in patients with very low sphincter pressures, with the complicating features of movement and respiratory artefact.

Previous studies have shown that refluxed acid is cleared from the oesophagus by peristaltic contractions[21]. The delay in time from the onset of the reflux episode to the first peristaltic contraction and the decreased peristaltic wave frequency found in patients with erosive oesophagitis indicate an abnormality in oesophageal acid clearance. This clearance defect was particularly evident in those subjects who also had abnormal oesophageal body motility. It is still not clear whether this abnormality is the result of a sensory or motor deficit and whether it is a primary abnormality or the result of the erosive oesophagitis. In those patients with normal oesophageal body motor function, the cause of erosive oesophagitis was clearly not abnormal acid clearance but excessive acid exposure through an abnormal LOS. Further studies are required to see whether motility-enhancing drugs are effective in the subgroup

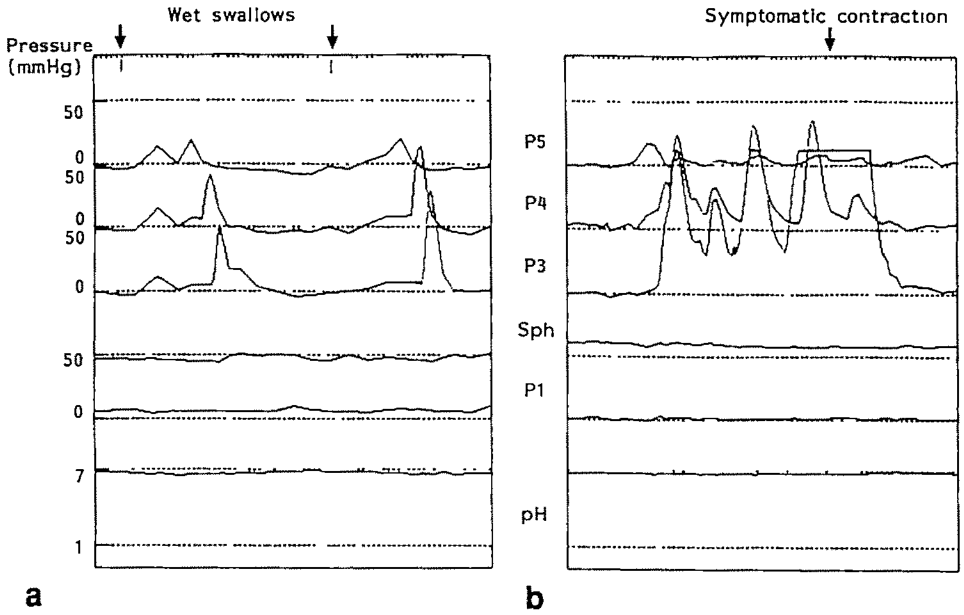

Figure 4 **a** *Normal standard motility test (station pull-through manometry) in a patient with chest pain showing* **b** *contraction wave of diffuse oesophageal spasm on 24-h study. P3–P5, oesophageal pressure transducers, Sph, sphinctometer; P1, gastric pressure transducer*

of patients with abnormal motor function. In addition, the effects of antireflux surgery in patients with an abnormal 24-h motility study merit explanation to see whether this abnormal motility can be influenced and how this might affect the symptomatic result.

The 24-h pH and motility study seems capable of improving diagnostic accuracy in oesophageal motor disorders compared with conventional oesophageal manometry. This was especially apparent for diffuse oesophageal spasm, where characteristic oesophageal contractions were noted only once during the standard test but were detected in seven patients by the 24-h study. Achalasia was diagnosed with the same frequency by both tests. The clinical relevance of the condition of non-specific oesophageal motor disorder is far from clear. While the diagnosis was more frequent in patients complaining of chest pain and/or dysphagia, there was not always a close correlation between the patient's symptoms and any specific abnormality. The same was true of nutcracker oesophagus, where most of the peristaltic contraction amplitudes seen in the only patient with this diagnosis were excessive yet rarely corresponded to event-marked episodes of chest pain.

Combined pH and motility recording with computerized automated data analysis has been found to be a useful clinical tool in the study of patients with chest pain and dysphagia In addition, it has provided new information on the pathophysiology of GORD under ambulant conditions.

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Physiological and metabolic responses to open and laparoscopic cholecystectomy

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This study examined respiratory function and metabolic and subjective responses in patients undergoing laparoscopic ($n = 10$) *and open* ($n = 11$) *cholecystectomy for chronic cholecystitis and biliary colic. Patient groups were matched for age, sex, weight and height. The duration of operation was similar in both groups. Respiratory function tests (vital capacity, forced expiratory volume in 1 s, peak flow and arterial blood gases), urinary cortisol, vanillylmandelic acid, metanephrines and nitrogen loss, serum complement component C3 and C-reactive protein (CRP), full blood count, erythrocyte sedimentation rate (ESR) and subjective responses as assessed on a pain analogue scale and by analgesic usage were determined for up to 48 h after surgery. Deterioration in perioperative respiratory function was significantly less for laparoscopic surgery. Arterial blood gas determinations indicated a greater perioperative decrease in arterial pH, with carbon dioxide retention in patients undergoing open cholecystectomy* ($P < 0\cdot02$), *reflecting poorer respiratory performance. Hormonal profile changes demonstrated an increase in urinary vanillylmandelic acid in the laparoscopic cholecystectomy group* ($P < 0\cdot04$); *no differences were detected in urinary cortisol, metanephrine or nitrogen excretion. Acute-phase responses were greatest in patients undergoing open cholecystectomy as determined by ESR and CRP level* ($P < 0\cdot02$ *and* $P < 0\cdot003$, *respectively). Pain and analgesic usage were significantly decreased in the laparoscopic cholecystectomy group* ($P < 0\cdot0009$ *and* $P < 0\cdot0001$), *which led to a decreased hospital stay after operation in these patients* ($P < 0\cdot0001$). *These data indicate improved respiratory and subjective responses and diminished acute-phase responses associated with laparoscopic surgery. Catabolic hormone release may, however, be increased.*

Laparoscopic cholecystectomy has become the operation of choice for uncomplicated gallstones[1]. The absence of a substantial skin incision appears to decrease patient discomfort, to shorten the period of hospitalization, and hasten recovery[2,3]. The laparoscopic approach also improves perioperative respiratory function[4] and it has been postulated that the absence of a wound may diminish the catabolic response to surgery[5].

It is currently unknown whether laparoscopic surgery does alter metabolic responses. However, the laparoscopic approach to gallbladder surgery now allows us to examine the influence of the wound on physiological responses to cholecystectomy. The purpose of this study was to compare respiratory, metabolic and subjective responses in two similar unselected groups of patients undergoing open and laparoscopic cholecystectomy to determine the contribution of the surgical wound to these responses.

Patients and methods

The rapid introduction of laparoscopic cholecystectomy into the majority of hospitals in Ireland has led to ethical constraints that preclude a randomized trial For this reason an unselected group of patients undergoing laparoscopic cholecystectomy in one hospital was compared with a group undergoing open cholecystectomy in another. Patient details are shown in *Table 1*.

The indication for surgery was chronic cholecystitis in all cases. Anaesthetic and operative procedures were standardized for each group. Anaesthetic agents used were thiopentone (May and Baker, Dagenham, UK) or propofol (ICI Pharmaceuticals, Macclesfield, UK) for induction and isoflurane (Anaquest, Swindon, UK) or propofol and fentanyl (Janssen Pharmaceuticals, Wantage, UK) and/or papaveretum (Roche Products, Welwyn Garden City, UK) for maintenance. Muscle blockage was with atracurium besylate (Calmic Medical Division, Crewe, UK) and reversed with neostigmine bromide (Roche Products) and glycopyrrolate (A. H. Robins, Horsham, UK). All open cholecystectomies were performed through an upper midline incision. In patients undergoing open cholecystectomy, peroperative cholangiography was performed routinely; no patient in this series required common bile duct exploration The laparoscopic group underwent surgery using a method that has been described previously[2]; cholangiography was not performed in these patients. Postoperative

Table 1 *Characteristics of patients undergoing cholecystectomy*

	Laparoscopic cholecystectomy ($n = 10$)	Open cholecystectomy ($n = 11$)	*P*†
Age (years)*	50·4(5·2)	47·5(4·5)	0·67
Sex ratio (M:F)	3:7	3:8	—
Body mass index (kg/m^2)*	31 7(5·6)	28 2(1·7)	0·45
Cigarettes smoked per day*	4·5(2·0)	5·8(2·6)	0·71
Operative time (min)*	83·8(10·0)	80·6(8·8)	0·81

*Values are mean(s.e.m). Body mass index = weight/height^2. †ANOVA

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opiate intramuscular analgesia was given to all patients as required, surgery in all cases was uneventful with no major postoperative sequelae in either group.

Respiratory responses

Pulmonary function studies were performed on a spirometer (Vitalograph, Maids Moreton, Bucks, UK). Vital capacity (VC) and forced expiratory volume in 1 s (FEV_1) were measured in the 24-h period before surgery and 24 h after operation Peak flow (PF) readings were carried out with a hand-held Wright peak flowmeter before operation and 24 h after surgery Arterial blood gases were drawn before operation and 12 h afterwards; pH, and arterial partial pressures of oxygen (P_{aO_2}) and carbon dioxide (P_{aCO_2}) were recorded.

Metabolic responses

Urine collections were taken for 24 h, beginning at the time of urethral catheterization at the start of the operation. Aliquots were taken for urea determination (Analyser IL 508, Instrumentation Laboratory, Milan, Italy). Estimation of nitrogen loss was calculated on the assumption that urea loss comprises 80 per cent of total nitrogen loss Aliquots of urine from the 24-h collection were also taken for measurement of levels of urinary cortisol and the catecholamine breakdown products vanillylmandelic acid (VMA) and metanephrines. Cortisol was measured by radioimmunoassay (Beck and Dickenson, Orangeburg, New York, USA), VMA was extracted using organic chemicals and quantified spectrometrically[6] Urine for metanephrine analysis was passed down catecholamine columns, sodium metaperiodate was added to the eluate and this then quantified spectrometrically (Biorad, Munich, Germany) Acute-phase responses were measured by erythrocyte sedimentation rate (ESR; Westergren method) 24 h after surgery; levels of the complement component C3 and C-reactive protein (CRP) were determined 24 and 48 h after operation. C3 was measured by radial immunodiffusion with Behring NOR plates (Hoechst, Dublin, Ireland) and CRP using a semiquantitative latex agglutination slide test (Human, Taunusstein-Neuhof, Germany) These investigations were performed in one laboratory.

Subjective responses

Pain was measured on a linear analogue scale every 12 h for 48 h after surgery and the numerical scores summed. Patients were not shown their previous responses. Analgesic usage was recorded as the total number of intramuscular opiate injections required after surgery Finally, hospital stay after operation was determined for all patients.

Statistical analysis

Results are expressed as mean(s.e.m.) and statistical comparisons made by one- or two-way analysis of variance (ANOVA). Linear regression analysis was performed by the method of least squares.

Results

Gallstones were present in all the gallbladders from both patient groups and chronic cholecystitis was confirmed histologically in all cases.

Respiratory responses

Results of pulmonary function studies and arterial blood gas determinations are shown in *Table 2*. The perioperative decreases in VC, FEV_1 and PF at 24 h were all significantly

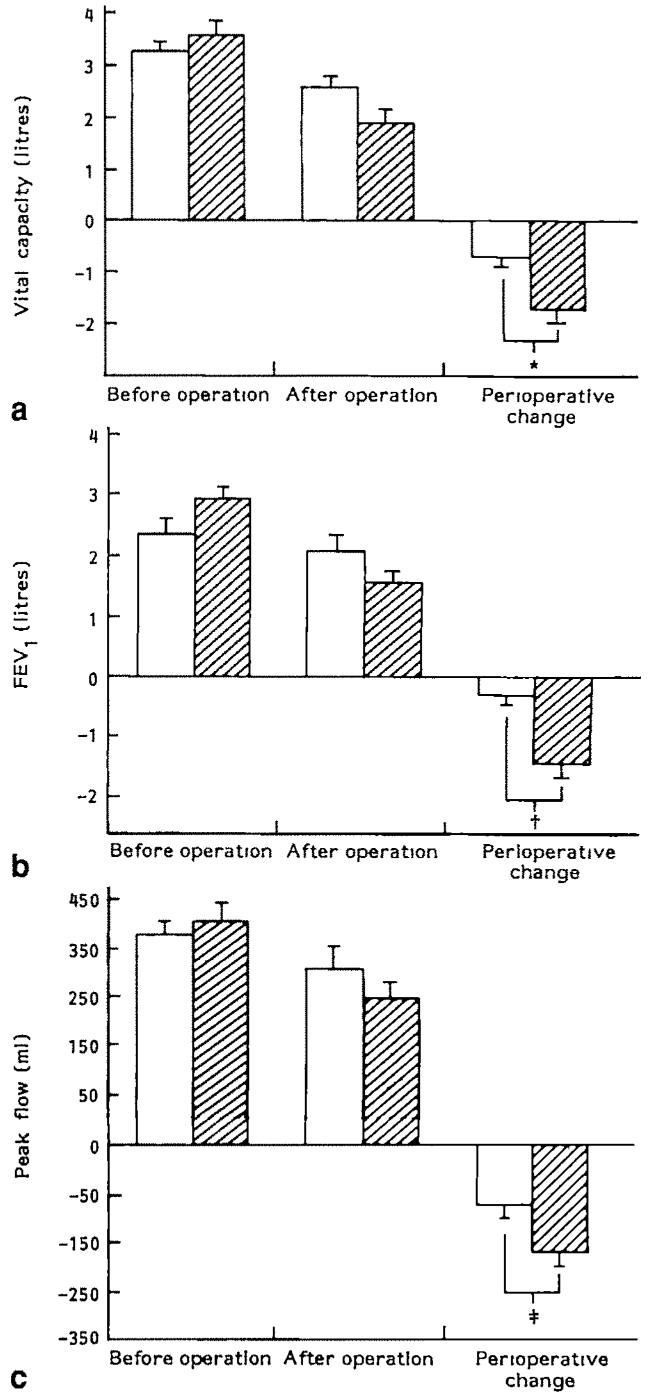

Figure 1 **a** *Vital capacity*, **b** *forced expiratory volume in 1 s* (*FEV_1*) *and* **c** *peak flow in laparoscopic* (□) *and open* (■) *cholecystectomy groups. Values are mean(s.e.m.).* *P < *0·007,* †P < *0·002,* ‡P < *0·02* (*ANOVA*)

Table 2 *Pulmonary function and arterial blood gases before and after cholecystectomy*

	Laparoscopic cholecystectomy			Open cholecystectomy		
	Before surgery	After surgery	Perioperative change	Before surgery	After surgery	Perioperative change
VC (litres)	3·25(0·20)	2·55(0·24)	−0·70(0·16)	3·59(0·24)	1·88(0·25)	−1·71(0·28)*
FEV_1 (litres)	2·37(0·24)	2·08(0·29)	−0·29(0·16)	2·95(0·21)	1·55(0·21)	−1·40(0·25)*
PF (ml)	378·7(29)	311·8(48·7)	−66·9(30·3)	406·0(40)	251·1(33·4)	−178·9(28·3)
pH	7·403(0·008)	7·395(0·009)	−0·007(0·11)	7·400(0·008)	7·333(0·02)†	−0·067(0·19)†
P_{aO_2} (kPa)	12·9(0·7)	10·5(0·69)	−2·3(0·87)	12·6(0·7)	9·3(0·5)	−3·3(0·7)
P_{aCO_2} (kPa)	5·4(0·2)	5·5(0·1)	0·06(0·15)	5·2(0·1)	5·9(0·2)†	0·73(0·22)†

Values are mean(s.e.m.) VC, vital capacity; FEV_1, forced expiratory volume in 1 s, PF, peak flow; P_{aO_2}, arterial partial pressure of oxygen; P_{aCO_2}, arterial partial pressure of carbon dioxide. *$P < 0·006$; †$P < 0·02$ (ANOVA)

Table 3 *Metabolic responses to cholecystectomy*

	Laparoscopic cholecystectomy	Open cholecystectomy
Urine		
Nitrogen loss (g/day)	8·4(1·2)	7·5(2·4)
Cortisol (μmol/day)	1·46(0·46)	1·16(0·28)
Metanephrines (mg/day)	0·39(0·08)	0·33(0·04)
VMA (μmol/day)	30·4(3·6)	20·4(2·1)*
Blood		
ESR (mm)	13·2(2·7)	26·6(4·3)†
Complement C3 (g/l)		
24 h	0·91(0·06)	1·00(0·04)
48 h	1·01(0·07)	1·02(0·06)
CRP (mg/l)		
24 h	15·8(5·2)	76·4(14·0)‡
48 h	20·6(5·5)	106·9(30·9)*

Values are mean(s.e.m.) VMA, vanillylmandelic acid; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. *$P < 0·04$; †$P < 0·02$, ‡$P < 0·003$ (ANOVA)

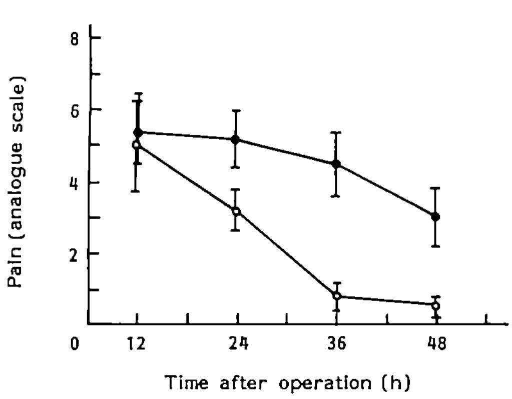

Figure 2 *Pain after operation* versus *time in laparoscopic* (○) *and open* (●) *cholecystectomy groups. Values are mean(s.e.m.).* P < *0·0009 (ANOVA)*

Table 4 *Pain scores, opiate requirements and hospital stay after cholecystectomy*

	Laparoscopic cholecystectomy	Open cholecystectomy
Pain (analogue scale)	9·7(1·5)	19·7(3·2)*
Opiate usage (no. of doses)	1·6(0·3)	7·8(0·7)†
Hospital stay after operation (days)	3·2(0·3)	6·1(0·4)†

Values are mean(s.e.m.) *$P < 0·0009$, †$P < 0·0001$ (ANOVA)

less in the laparoscopic cholecystectomy group ($P < 0·006$) (*Figure 1*). Blood gas data demonstrated a significantly greater decrease in arterial pH and rise in $P_{a\text{CO}_2}$ in patients undergoing open cholecystectomy compared with those having the laparoscopic procedure ($P < 0·02$ and $P < 0·03$ respectively). No significant difference between the groups was detected in perioperative arterial $P_{a\text{O}_2}$ change. There was a negative correlation between both the perioperative change in pH and $P_{a\text{CO}_2}$ level and total pain scores ($R^2 = 0·22$, $P < 0·05$; $R^2 = 0·37$, $P < 0·008$).

Metabolic responses

There was no significant difference between the groups in 24-h urinary nitrogen loss after surgery (*Table 3*). The 'stress hormone' cortisol and the catecholamine breakdown products measured in 24-h urine collections after surgery were all increased in the laparoscopic cholecystectomy group (*Table 3*). However, only differences in VMA levels were significant ($P < 0·04$). Acute-phase responses are also shown in *Table 3* and demonstrate increases in ESR 24 h after surgery ($P < 0·02$) and in CRP at 24 and 48 h after surgery ($P < 0·003$ and $P < 0·04$ respectively) in patients undergoing open cholecystectomy. No significant changes occurred in C3 levels. The ESR 24 h after surgery correlated significantly with CRP levels ($R^2 = 0·31$, $P < 0·03$).

Subjective responses

Total pain (*Figure 2*) and opiate analgesia usage were significantly decreased in the laparoscopic cholecystectomy group ($P < 0·0009$ and $P < 0·0001$ respectively) (*Table 4*). Hospital stay after surgery was significantly shorter in patients having laparoscopic rather than open cholecystectomy ($P < 0·0001$) (*Table 4*).

Discussion

Elective surgical wounds and trauma elicit similar physiological responses; these include increased stress hormone release, alterations in intermediate metabolism and fluid balance, negative nitrogen balance and increased hepatic production of acute-phase proteins. Understanding of these processes has advanced rapidly in recent years and it appears that both afferent neural stimuli and circulating factors are responsible[7]. Attention has now focused on attenuating these responses, which can be detrimental if excessive, mainly because of loss of peripheral muscle or lean body mass. Afferent neural stimuli can be blocked with epidural anaesthesia[8]. However, blockage of circulating factors such as catabolic hormones, cytokines, leukotrienes and eicosanoid and prostanoid mediators that are released by the wound or other areas of tissue trauma is potentially more difficult to achieve.

Minimally invasive surgery may present an alternative approach to diminishing metabolic responses by the avoidance of a substantial abdominal incision, which in elective surgery is frequently the site of maximum tissue damage. Laparoscopic cholecystectomy, therefore, provides a means for determining the contribution of the wound to physiological responses to surgery. Unfortunately, the rapid introduction of this procedure into most hospitals in Ireland has resulted in ethical constraints in conducting a randomized trial. For this reason the present study examined two groups of unselected patients undergoing open and laparoscopic cholecystectomy in two different hospitals. Notwithstanding the constraints of such an approach, both groups were well matched for age, size and smoking habits. Of interest, the duration of operation was similar in both groups, which may be because laparoscopic surgery was well established at the beginning of the study; furthermore, peroperative laparoscopic cholangiography was not performed, which further limited the duration of surgery in this group.

Abdominal surgery is associated with deterioration in lung function, which predisposes to lower-lobe atelectasis[9]. This study confirms improved perioperative respiratory performance with laparoscopic in comparison with open surgery. The decreases in VC, FEV_1 and PF up to 24 h after surgery were all significantly improved with the laparoscopic procedure. Associated with this was a smaller drop in arterial pH and carbon dioxide retention 12 h after surgery. Carbon dioxide 'retention' related to pneumoperitoneum may lead to respiratory embarrassment in the operative period in patients with impaired cardiopulmonary function[4]. It is unlikely, however, that hypercapnia induced by pneumoperitoneum would persist for several hours after surgery. Because of the relatively small number of patients in this study no attempt was made to correlate respiratory function with clinical events, so it is not known whether better perioperative pulmonary performance leads to decreased pulmonary morbidity rates. The improved perioperative respiratory function demonstrated in this study is likely to result from decreased patient discomfort: this is supported by the significant correlation between the total pain score and initial arterial pH and carbon dioxide changes

For critically ill patients one of the most significant metabolic events is the magnitude and duration of negative nitrogen balance, which reflects erosion of lean body mass[10,11]. In this study, no difference was detected in urinary nitrogen loss between the two groups as measured by urea nitrogen estimation in the first 24 h after surgery. However, it would be surprising to detect differences over such a short interval in patients undergoing surgery of this magnitude. Nitrogen balances were not calculated because of the difficulty of estimating the nitrogen content of ward foodstuffs. It must be considered, however, that oral intake was minimal in patients undergoing open cholecystectomy whereas the majority of those having laparoscopic cholecystectomy started to eat within 24 h of surgery. This would therefore influence nitrogen balance in favour of the laparoscopic group in the short term.

The stress hormones cortisol and adrenaline/noradrenaline are two of the major counter-regulatory hormones that oppose the action of insulin and promote muscle catabolism[12]. Levels of both hormones are increased after major surgery or injury[13]. Because of difficulties in assaying these hormones, 24-h urine collections were measured. Both cortisol and the catecholamine breakdown products were increased in laparoscopic cholecystectomy in comparison with the open procedure; however, only VMA levels demonstrated significant differences. This unexpected finding could reflect afferent neural stimulation from the pneumoperitoneum, which may be a potent stimulant of the stress hormone response Attenuation of this response is of limited physiological benefit in the setting of relatively minor surgery but might be tested by examining the effects of epidural anaesthesia on stress hormone responses.

Hepatic acute-phase protein production is another important feature of the response to surgery, trauma and sepsis[14]. Both postoperative ESR at 24 h and CRP levels at 24 and 48 h were significantly raised in open compared with laparoscopic cholecystectomy, indicating a greater inflammatory response in the former group. It should be noted that open cholecystectomy was accompanied by intraoperative cholangiography whereas laparoscopic cholecystectomy was not; we believe, however, that it is unlikely that this procedure would influence the magnitude of change seen in acute-phase responses demonstrated in this group. ESR and CRP levels were also significantly correlated, suggesting that the latter is a sensitive indicator of the inflammatory response[15]

The diminished acute-phase response to laparoscopic cholecystectomy independent of normal or increased stress hormone release implies independent regulation of the components of the physiological response to surgery. This may result from decreased release from a smaller wound surface of specific circulating factors such as the cytokine interleukin 6, levels of which are known to increase following surgery[16] and which is an important inducer of hepatic acute-phase protein responses[17]. Corresponding changes in the levels of interleukin 1 and tumour necrosis factor, the two other major proinflammatory cytokines and potent stimulants of stress hormone release, may also occur. However, any diminution in release may be offset by afferent stimuli induced by pneumoperitoneum[18,19]. Measurement of levels of these circulating factors, while difficult, now needs to be performed to determine the specific role, if any, of these agents in the metabolic events described.

Apart from significant differences in the physiological responses to laparoscopic and open cholecystectomy, it is clear from this study that subjective responses were also significantly improved after laparoscopic surgery, as previously demonstrated by others[2,20]. This is reflected in a shorter postoperative hospital stay.

Metabolic assessment of laparoscopic surgery increases our knowledge of the contribution of the wound to physiological responses to surgery. Greater understanding of the components of these responses and their initiating stimuli may eventually allow their manipulation to the benefit of critically ill patients.

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Psychomotor testing and the ability to perform an anastomosis in junior surgical trainees

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Ten junior surgical trainees underwent objective testing of manual dexterity and visuospatial ability and were required to carry out five consecutive anastomoses on fresh porcine jejunum. Anastomoses were scored by a single observer and a cumulative error score (CES) derived for each procedure. In the first anastomosis there was little correlation between the psychomotor test results and the anastomosis scores. In subsequent trials there were significant negative correlations between aspects of manual dexterity and the CES. Over the five anastomoses there were significant negative correlations between improvement and manual dexterity, but there was a positive correlation between improvement and visuospatial ability ($r_S = 0{\cdot}76$, $P < 0{\cdot}005$). Visuospatial skills are more important than pure motor ability in predicting the capacity to perform an anastomosis and tests of manual dexterity may be misleading in this context.

Surgical technique is important[1–3] and, although technical ability is not the only quality required to be a good surgeon, few would argue that it does not represent a necessary attribute. It has been suggested that those aspiring to a career in surgery should undergo aptitude testing before admission[4], and such assessment has been used to select trainees in the Netherlands[5]. Despite attempts to develop objective methods of assessing surgical skill, there is little evidence to support the use of 'psychomotor' or 'neuropsychological' tests to predict an individual's ability to be a surgeon or carry out basic surgical tasks.

In this study junior surgical trainees underwent simple tests of manual dexterity, hand–eye coordination and visuospatial ability. They also carried out simulated anastomoses, which were scored independently for quality of performance and finished result. The scores from the objective tests were then compared with those obtained from the anastomoses to determine whether the ability to carry out a fundamental surgical task could be predicted.

Methods

Ten surgical senior house officers without significant experience of anastomotic technique were studied. There were nine men and one woman, of mean age 26·5 (range 25–29) years. None had completed more than 6 months of training in general surgery; the total duration of training following house officer posts varied from 1 to 36 months. All were right-handed.

After a full explanation of what the study entailed, each trainee carried out three psychomotor tests: the Crawford small parts manual dexterity test[6], the Gibson spiral maze test[7] and the hidden figures test[8]. The Crawford test (inserting small nails into an array of holes with a forceps and threading screws into matching holes with a screwdriver) provides a measure of fine motor ability (manual dexterity) and yields two scores: the time taken to locate the nails and screws respectively in their correct positions. The maze test gives a further indication of hand–eye coordination by means of drawing through a spiral maze while simultaneously avoiding obstacles. Again, two scores are obtained, the first being the time taken and the second consisting of the number of errors. The hidden figures test, which requires the identification of shapes within complex arrangements of lines, assesses visuospatial ability and is scored as the number of correct detections made in 10 min. The tests overall take approximately 25 min to perform.

On a separate occasion, the trainees were instructed in the performance of a small bowel anastomosis using a single layer of interrupted serosubmucosal 3/0 braided nylon. They then carried out five simulated anastomoses using porcine jejunum. These were scored by a single observer using the criteria of Stotter and others[9]

1. Time taken in minutes.
2. An arbitrary 'clumsiness' score that takes into account unproductive movements, fumbles and gross errors during the performance of the anastomosis. This was scored on a 10-cm visual analogue scale that ranged from 0 (perfect) to 100 (hopeless).
3. An 'anastomosis score' in which the completed anastomosis was scored from 1 to 3 for each of five characteristics: suture spacing; knots; overall tidiness, integrity of the anastomosis using inflation with a 10-cm head of water; and accuracy of suturing in terms of extramucosal placement.

From these scores, a cumulative error score (CES) was derived from the sum of the clumsiness score, the time taken in minutes, and 2 × (15 – the anastomosis score). This scoring system was chosen as the CES improved over the course of five anastomoses and remained constant thereafter[9]. The effect of practice could therefore be studied over a short time span. The statistical significance of all correlations studied was tested using Spearman's rank correlation coefficient (r_s).

Results

The CES for each anastomosis trial showed a consistent improvement over the five attempts (*Figure 1*). The mean scores

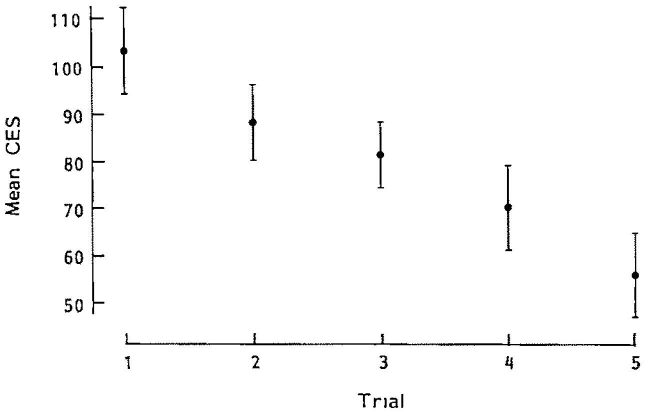

Figure 1 *Improvement in the mean cumulative error score (CES) over the five anastomosis trials. Values are mean(s.e.m.) for the ten trainees*

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Table 1 *Spearman rank correlation coefficients between psychomotor tests and suturing ability on the anastomosis trials*

	Dexterity		Maze		
	Nails (min)	Screws (min)	Time (s)	Errors (no.)	Hidden figures score
Correlation coefficient					
Trial 1 CES	0·37	−0·40	−0·37	0·33	−0·04
Trial 2 CES	−0·03	−0·69‡	−0·48	0·11	−0·25
Trial 3 CES	−0·24	−0·62†	−0·21	0·01	−0·35
Trial 4 CES	−0·03	−0·57†	−0·37	0·10	−0·21
Trial 5 CES	0·08	−0·67‡	−0·41	0·08	−0·24
Difference in CES (trial 1 − trial 5)	0·57†	0·20	0·07	0·57†	0·76§
Test result*	4·3(0·6)	6·9(1·3)	47·1(4·5)	2·0(0·7)	5·8(3·4)

*Values are mean(s.d.). CES, cumulative error score. †$P < 0{\cdot}05$; ‡$P < 0{\cdot}03$; §$P < 0{\cdot}005$

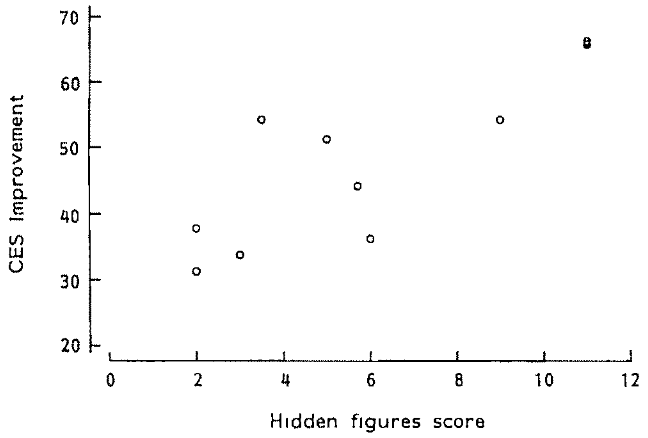

Figure 2 *Correlation between the score on the hidden figures test and the improvement in the cumulative error score (CES) over the five anastomoses* ($r_S = 0{\cdot}76$, $P < 0{\cdot}005$)

on the psychomotor tests and the correlation coefficients between these scores and the CES on each of the anastomosis trials are given in *Table 1*. This table also shows the degree of association between the score on each test and the rate of improvement in the CES from the first to the fifth anastomosis.

For the manual dexterity task there were generally negative correlations between the time taken to insert the screws and the ability to perform the anastomosis trials. In four of the five attempts, the coefficients were statistically significant, indicating that the trainees who carried out the task relatively quickly produced worse results on the surgical simulations. No significant correlations were seen between the CES for the individual anastomoses trials and the scores on either the maze test or the hidden figures test.

There were correlations between the psychomotor test results and the rate of improvement in anastomotic technique (derived by subtracting the CES on the final anastomosis attempt from that on the first). Analysis of the Crawford dexterity test showed that those who were fastest at completing it were those who displayed less improvement with practice on the surgical task. Those with lower error scores on the Gibson maze test tended to improve to a lesser extent. There was a positive correlation ($r_S = 0{\cdot}76$, $P < 0{\cdot}005$) between the ability to detect hidden figures and the degree to which anastomosis skills improved (*Figure 2*)

Discussion

The importance of technical skill in surgery is self-evident[10], and for a trainee to embark on a surgical career only to find that he or she is hampered by a lack of ability that cannot be improved by practice or training may be demoralizing. It is known that the results of surgery are highly operator dependent[11,12], and if such a trainee progresses to any extent, patients may suffer. It would therefore seem sensible to try to predict technical skill at an early stage. Surgeons are currently selected on the basis of examinations that are poor indicators of clinical performance[13–15].

Manual dexterity appears to be a useful starting point in the quantification of what is essentially a manual skill. A study from the USA, however, failed to show that manual dexterity had any significant association with subjective assessments of surgical skill[14]. Consultant surgeons perform significantly worse than trainees in manual dexterity tests, and there is no difference between surgeons and physicians[16]. The present study concurs with these findings, and it is likely that variations in skill represent variations in more subtle abilities that are superimposed on a necessary minimum level of dexterity.

Another method for predicting skill may be to measure visuospatial ability. This can be defined as 'the ability to keep in mind a definite configuration so as to identify it in spite of perceptual distractions'[17]; the hidden figures test is a well validated method of quantifying this attribute[8,18]. Although spatial ability is not related to general academic achievement[14,18], it has been shown to correlate positively with ability at school geometry, quantitative thinking, shop mechanics, watch repair and aviation skills[19,20]. In three studies of surgical residents, spatial ability was found to be significantly related to consensus ratings of technical surgical skill provided by senior staff members[14,21,22].

To date, all psychomotor testing on surgeons has been correlated with surgical skill as measured by the subjective opinions of senior surgical staff. A trainer's attitude to a trainee, however, may be coloured by factors not dependent on technical skill[23]. In the present study this 'interference' has been minimized by scoring an isolated surgical task. The findings confirm the impression that visuospatial ability is related to technical skill and to the ability to improve with practice.

Two important questions arise from this study: 'Can visuospatial skill be taught?' and 'Do potential surgeons select themselves based on an unconscious appreciation of their own spatial ability?'. The answers to these questions have implications for the implementation of selection procedures based on psychomotor testing If the answer to either is positive then such an approach would be inappropriate. There are several indications that visuospatial ability is inherent and not susceptible to training[22,24,25], although it may still underlie the process of self-selection.

It is unrealistic to think that success in surgery can ever be predicted solely by objective psychological tests. However, especially in this era of minimally invasive surgery where three-dimensional inferences must be made from a two-dimensional image, non-academic selection procedures might be used to screen candidates wishing to enter a surgical career Potentially gifted individuals should not be excluded on the basis of inappropriate tests and new assessment techniques must be validated before they are introduced.

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Prospective randomized trial comparing the Shouldice technique and plication darn for inguinal hernia

The lowest recurrence rates after inguinal hernia repair have been achieved by specialized hernia clinics. The Shouldice repair achieves success through application of a meticulous standardized operation carried out by specialist hernia surgeons. In a trial designed to rule out surgeon-dependent variables, 322 inguinal hernias were randomized prospectively to Shouldice repair or plication darn. Fifteen general surgeons operated on 322 patients. Fourteen surgeons in training not familiar with Shouldice repair received constant supervision for six repairs before independent operation. The mean(s.d.) patient age was 58·3(1·5) (range 20–84) years for Shouldice repair and 57·0(1·2) (range 18–85 years) for plication darn. The sex ratio (M:F) was 17:1 and right side to left side ratio 1·8:1. Six-week complication rates for wound infection (Shouldice repair, 5 per cent; plication darn, 4 per cent) and haematoma (Shouldice repair, 7 per cent; plication darn, 5 per cent) were similar in both groups. There were a similar number of sliding hernias in the Shouldice repair (14) and plication darn (20) groups. After a mean follow-up of 30 (range 24–48) months there were seven recurrences in the Shouldice group and four in the plication darn group ($P > 0·05$)*. The recurrences suggest that additional supervision of junior surgeons is required during the Shouldice repair learning period.*

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Groin hernias occur in 3–8 per cent of the population and account for 12·5 per cent of all surgical admissions[1]. Operation failure after inguinal hernia repair remains a significant problem: of the 80 000 inguinal hernia repairs carried out annually in the UK, 10 per cent are for recurrent hernia. Whereas hernia specialists report recurrence rates of between 1 and 5 per cent for primary inguinal hernias, those from non-specialist centres are in the region of 5–20 per cent[2]. The results of 200 000 patients operated on in the Shouldice clinic have been widely publicized, but fewer than 20 per cent of consultant surgeons in the UK employ the Shouldice method alone or in combination with other techniques[3].

The most popular technique employed by UK surgeons is a corruption of the repair described by Bassini. In his original description to the Italian Society of Surgeons in Genoa in 1887, Bassini described complete division of the external oblique and the transversalis fascia with construction of a new floor of the inguinal canal[4]. A number of modifications have been introduced under the Bassini eponym. Routine division of the floor of the canal by incising the transversalis fascia has been abandoned in favour of a more conservative operation with superficial plication of the transversalis fascia around the undisturbed cord combined with an overlay darn between the conjoint tendon and inguinal ligament. This operation of plication darn is employed by most consultant surgeons in practice in the UK[3]. Even modern improvements in the Moloney-type darn produce recurrence rates inferior to those of the Shouldice repair[5].

The Shouldice operation is a modern revival of the original Bassini procedure with excision of the cremaster, overlapping of the divided transversalis fascia and multilayer closure using monofilament suturing[6]. Recurrence rates at 10 years in the hands of many hernia specialists are 1 per cent or less[7–10]. Even allowing for the advantages of herniorrhaphy carried out in specialist centres, Shouldice repair is seven times more efficient in avoiding recurrence compared with the well documented Cooper ligament repair carried out in a single centre[11].

Patients and methods

Patients admitted under the care of one consultant surgeon between October 1987 and October 1989 were eligible for entry into the trial. Informed consent was obtained before operation and those refusing consent were excluded. Patients were assigned to Shouldice repair or plication darn by random number in the operating theatre just before skin incision.

Previous experience has shown that junior surgeons adopting a new method of inguinal herniorrhaphy require close supervision during their first six operations[12]. Surgeons not familiar with the Shouldice operation were therefore closely supervised before operating independently. To avoid introducing other variables, only elective cases were entered into the study and all operations were carried out under general anaesthesia.

Because trainees were familiar with plication darn, this technique acted as a control operation for comparison with Shouldice repair. Plication darn involved imbrication of the undisturbed transversalis fascia, combined with an overlay darn of at least two layers between the conjoint tendon and the inguinal ligament. Because of the increased risk of urinary retention and scrotal oedema associated with simultaneous bilateral hernia repair, patients with two hernias underwent sequential procedures with at least 6 weeks between the two operations[13,14].

All patients were followed up prospectively by clinical examination by a consultant or surgical registrar and by pro forma in a dedicated hernia clinic until October 1991, i.e. for at least 2 years. Clinical examination was carried out at intervals of 6 months after the first postoperative check at 6 weeks.

Statistical analysis was performed using the χ^2 test.

Results

Sex and type of hernia were distributed equally between patients undergoing Shouldice repair and plication darn (*Table 1*). The mean hospital stay was 2·9 days in both groups, 82·3 per cent of patients were discharged at 2 days and longer admissions were usually for social reasons, except for one patient with a scrotal haematoma (inpatient stay 14 days). The majority of complications were minor (*Table 2*). There was one myocardial

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Table 1 *Patient details*

	Shouldice repair (n = 151)	Plication darn (n = 171)
Sex ratio (M.F)	145:6	159.12
Age (years)		
Mean(s.d.)	58·3(1·5)	57·0(1·2)
Range	20–84	18–85
Type of hernia		
Direct	47	53
Indirect	84	92
Sliding	14	20
Irreducible	8	9
Combination	10	12
Mean hospital stay (days)*	2·9	2·9

*Overall, 82·3 per cent discharged at 2 days

Table 2 *Complications*

	Shouldice repair (n = 151)	Plication darn (n = 171)
Haematoma	11	8
Wound infection	7	6
Chest infection	1	1
Myocardial infarction	1	1
Paraesthesia	1	1

Table 3 *Operator details*

	Shouldice repair (n = 151)	Plication darn (n = 171)
Consultant	25	23
Senior registrar	61	82
Registrar or senior house officer	65	66

Table 4 *Follow-up and recurrence*

		Recurrence	
Follow-up	No	Shouldice repair (n = 151)	Plication darn (n = 171)
6 weeks	302	2	0
6 months	282	4	2
12 months	261	0	1
24 months	224*	1	1
36 months	133	0	0
48 months	61	0	0

*This represents 70 per cent of patients followed for 2 years

infarction after operation in each group and one patient in each experienced persistent wound pain or paraesthesia

One consultant surgeon and 14 junior surgeons performed the operations with an even distribution between Shouldice repair and plication darn (*Table 3*). No junior surgeon was allowed to participate in the study until six consultant-supervised Shouldice operations had been performed. Subsequently, when a junior surgeon was supervised by a more senior surgeon, the operation was attributed to the senior surgeon.

Follow-up to 24 months was achieved in 70 per cent of patients (*Table 4*). There was no significant difference in recurrence rate between the two groups at any time during follow-up. All recurrences were confirmed by the consultant who carried out the subsequent repair. No surgeon was responsible for more than two recurrences, all of which resulted from posterior wall failure, indirect sacs having been dealt with effectively. The operation of choice for repair of recurrence employed a preperitoneal approach using prosthetic mesh.

Discussion

This trial has not shown superiority of Shouldice repair over plication darn. The recurrence rate[15] at 2 years was 4 per cent for Shouldice repair and 1·8 per cent for plication darn, which projects to a recurrence rate of 10 and 4·5 per cent respectively at 25 years. Only one of the 11 recurrences was attributable to the consultant surgeon, who had a 10-year experience with the Shouldice operation, and it must be concluded that the high failure rate of the operation was attributable to inexperience with this technique in the junior surgeons. The results of such surgeons are almost identical to those achieved in a recently published trial of day-case inguinal hernia repair by junior surgeons[16].

The excellent results of the Shouldice operation have been reported by several hernia specialists. The applicability of this technique to surgeons in general or surgeons in training has never been tested in a prospective randomized trial. Intense debate has centred on whether a standardized approach imposing great precision in operative technique is more important than skilled surgeons applying a variety of procedures[17–19]. At the Shouldice clinic, new staff surgeons receive close supervision for the first 50 herniorrhaphies and do not operate independently until they have repaired 100 inguinal hernias. The second assessment of operative technique is made after the first 1000 hernias, and only after this assessment is the surgeon considered a fully fledged independent operator. The present supervision of only six herniorrhaphies was therefore clearly inadequate.

In a recent letter to this Journal from the San Josef Hospital, Vienna, Kux and Fuchsjager[20] indicated that they were undertaking a prospective randomized trial comparing Bassini and Shouldice repairs. Results of this trial have not yet been reported; patient entry was halted in 1989. No other clinical trial has prospectively compared Shouldice repair with other types of herniorrhaphy carried out by non-specialist surgeons.

Six recurrences caused by posterior wall failure occurred within 6 months of Shouldice repair. This finding implicates technical problems in reconstructing the completely divided floor of the inguinal canal. Inadequate repair of the posterior wall by plication darn appears to result in a more gradual weakening of the posterior wall, which becomes clinically apparent at a later stage. In the setting of a busy general surgical unit where junior surgeons received supervision for six Shouldice repairs before independent practice, recurrence was not diminished by utilizing this repair compared with plication darn. Examination of the reasons for technical failure of Shouldice repair suggests that the technical feature that needs to be most carefully taught is the layered reconstruction of the posterior inguinal wall.

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Inguinal herniotomy in young infants

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Ninety-two consecutive infants aged up to 12 months underwent primary inguinal herniotomy over a 5-year period. All were treated in a district hospital paediatric surgical unit according to recommendations of the British Association of Paediatric Surgeons. After a mean follow-up of 45·8 months, one patient had a failed repair and four (4 per cent) a hernia recurrence. One infant developed a wound infection. Infantile hernia can be managed safely and efficiently in a district hospital.

Congenital indirect inguinal hernia is a common paediatric condition[1,2]. Surgical management, especially in younger infants, requires special care[3–5] and is usually performed in specialist regional centres. The numbers of such centres are limited and the British Association of Paediatric Surgeons recommends that routine paediatric surgical work be performed by appropriately trained general surgeons in specialized units within district general hospitals[6] to cope with the high workload. This view has been supported by The Royal College of Surgeons of England but is not shared by everyone[7] and widespread implementation of the recommendation has been slow[8].

This study assessed the result of inguinal herniotomy in young infants in a district hospital unit to investigate the feasibility of the Association's recommendation

Patients and methods

Ninety-two patients (85 boys and seven girls aged up to 12 months) presenting between 1985 and 1990 with an inguinal hernia who underwent herniotomy were reviewed, using case notes and clinical follow-up

Eighty-six patients had a unilateral hernia and six bilateral hernias. Referral of the 92 infants was from numerous sources, as shown in *Table 1* Eleven referrals (12 per cent) were urgent, with the hernia being, or suspected to be, incarcerated All but one of these infants were treated by traction, repair of the reduced hernia was performed on the next available operating list, usually within 2 days One patient underwent emergency surgery because of small bowel strangulation. Elective cases were seen after a mean of 22 days from the time of referral, and the mean waiting time for operation was 27 days All infants were treated as inpatients, surgery was performed under general anaesthesia

The patients' mean age at the time of operation was 3 months (range 3·5 weeks to 12 months) with a mean weight of 6·1 (range 2·4–11·7) kg Of these infants, 31 (34 per cent) were born preterm, between 27 and 37 (mean 33·1) weeks of gestation Four (4 per cent) had a low birth-weight of <2500 g, and one was born at 1300 g Twenty-one patients (23 per cent) had neonatal problems (*Table 2*) All were fit at the time of surgery. Eighty-five repairs (87 per cent) were performed by a consultant and the rest by a registrar.

Infants were reviewed clinically after 4 weeks and all early complications recorded. Long-term assessment was conducted by clinical review with a study of the case notes. Wound problems, hernia recurrence, testicular atrophy and malpositioning in particular were sought and other problems noted

Results

In the follow-up of 8–76 (mean 45·8) months, surgically related complications were detected in six patients (7 per cent). Four developed a recurrent hernia after a median interval of 12 (range 10–26) months. Initial herniotomy was immediately unsuccessful in one boy aged 11 months with an unusual sliding hernia. One patient had a wound infection, the assessment of which was based on the working definition of a clinically inflamed or discharging wound which required active treatment. There were no perioperative deaths or anaesthetic complications.

Table 1 *Sources of referral*

Source	No of patients
General practitioner	51 (55)
Accident and emergency department	17 (18)
Paediatric department	14 (15)
Community health screening	10 (11)
Total	92 (100)

Values in parentheses are percentages

Table 2 *Neonatal problems in the study group*

Problem	No of patients
Jaundice	6
Respiratory distress requiring ventilation	5
Low birth-weight (<2500 g)	4
Severe immaturity	2
Cardiac abnormality	2
Anaemia	1
Hypocalcaemia	1
Total	21

Discussion

Infants who are born preterm or who have a low birth-weight exhibit a higher incidence of herniation[9–11] and a greater risk of perioperative morbidity and mortality[2–4] unless managed by an experienced surgical and anaesthetic team. Such routine paediatric surgery may be performed outside regional centres[6,8,12], but there has been debate over the safety aspects of doing so[7]. Reports involving older children have been submitted from community hospitals outside the UK[13]. The patient population in the present review did not differ significantly from those of other series Infants were referred from diverse sources and included healthy as well as higher-risk cases.

The main postoperative complication was hernia recurrence (occurring in 4 per cent); there was also one unsuccessful repair. Most published data (*Table 3*) come from older reports[14–18], mainly from the USA. The number of patients was not always clearly specified, and in some studies was small. One recent British series[19] recorded a recurrence rate of 3·5 per cent, linking technical error with the inadequate experience of junior surgeons.

The recurrences in the present series presented late, between 10 and 26 months after initial surgery. Two patients presented with an irreducible hernia and underwent surgery within 24 h. Although these hernias were reduced before operation, the tissue was still oedematous. As in the other two patients with recurrences (both under the age of 2 months), the sacs were friable and thin, and difficult to isolate back to the internal ring. These babies were operated on by the consultant. The

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Table 3 *Recurrence rates in published series of infantile herniotomy*

Reference	No of cases	Recurrence
Iason[14]	150	1* (0 67)
Coles[15]	9	1 (11)
Larsen[16]	12	0 (0)
Potts *et al.*[17]	100	0 (0)
Santulli and Shaw[18]	1294*	3 (0 23)
Harvey *et al*[19]	173	6 (3 47)

Values in parentheses are percentages. *Clear data not provided

non-recurrence complication rate of 1 per cent compares favourably with those of other series. There was no apparent testicular problem, although possible damage to the vas deferens was not examined.

As incarceration of the hernia is the main danger associated with delay in treatment[5,20] and potentially increased morbidity[21,22], expeditious treatment is essential. A mean of 49 days from referral to completion of management of elective cases was demonstrated in this study. Priority was given to the newborn. None of these infants developed incarceration and all urgent cases were treated promptly without increased morbidity.

This study demonstrates that reasonable results can be achieved with inguinal herniotomy in young infants in a specialized district hospital unit. The recommendation of the British Association of Paediatric Surgeons is supported.

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Comparative audit: an experimental study of 147 882 general surgical admissions during 1990

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In 1991, 1025 general surgical Fellows of The Royal College of Surgeons of England were circulated with a pro forma and asked to submit local audit results for admissions during 1990 to a confidential comparative audit service. The individual topics of cholecystectomy and colorectal resection were studied. Data returned by 160 surgeons concerned 147 882 admissions including 122 620 operations. Overall mortality rates ranged from 0 to 5 per cent and morbidity rates from 0 to 22 per cent. Laparoscopic cholecystectomy was associated with one-quarter of the mortality rate and two-thirds the morbidity rate of open cholecystectomy. Of the 33 surgeons who responded to a survey after the presentation of results, all wished to continue the exercise in future years; 39 per cent had been stimulated to perform further analyses and 15 per cent had changed practice habits as a result. Comparative audit involving large numbers of patients and surgeons is feasible and seems beneficial to participants.

Surgeons in the UK are required to audit practice. The ability to do this varies and is often dependent on the availability of suitable information technology[1,2]. When information is available an understanding of local practice may be reached[3]. Results may then need to be compared within a larger group. This stimulus produced comparative audit and provided the opportunity to define what is required of information systems[4].

Comparative audit deals with 'raw' data, the collection of which is largely uncontrolled. Unevenness in data collection is, however, compensated for by the large numbers of patients involved. Information from such databases can then be used for comparison with unit or personal results. If investigation indicates that poor practice is the cause of difference, corrective action can be instituted. Comparison of individual working conditions can be made, giving a greater insight into the special characteristics of local practice

A confidential comparative audit service was set up at The Royal College of Surgeons of England and a pilot meeting organized for general surgeons to develop, test and evaluate the methodology.

Materials and methods

A booklet pro forma was designed and circulated to all general surgical Fellows of The Royal College of Surgeons of England working in England and Wales. Information was requested on activity in 1990; a summary of the items requested is shown in *Table 1* The pro forma was circulated to 1025 surgeons at the end of March 1991 and completed returns requested by the end of April 1991. This time scale meant that only those with access to the data requested were likely to take part. Assurance was given that the data would be treated confidentially. A confidential number was allocated and all further handling of the data performed in connection with this number only Some members of the secretariat had access to the names of the surgeons but no surgeon was given this information. Participants were asked to enter 'n a.' where data were not available and '0' for a nil return.

Returned data were entered into a spreadsheet (Super Calc 5; Computer Associates, San Jose, California, USA). Each data item was ranked and means and 25, 50 and 75 percentiles produced. Sheets were produced for each confidential number and the rankings and positions on each of the forty analyses could be seen. An example chart is shown in *Figure 1*.

Analyses were made of the manpower available to consultants. Recommended manpower equivalent values for use in surgical audit and surgical workload analysis were those agreed by a working party[5] and are shown in *Table 2*

Surgeons graded their operations, where possible, into minor, intermediate and major according to the British United Provident Association classification[6] and this grading was converted into the intermediate procedure equivalent value[7] (*Table 3*) This enabled a weighted value to be produced for operative workload

Table 1 *Data requested in the pro forma sent to consultants*

- Resources
  - Manpower, beds, theatre sessions
- Workload
  - Admissions, emergencies, procedures, stay nights
- Case mix
  - Age groups, diagnoses, operative groups
- Complications
  - Mortality, complication grades and types
- Topics
  - Cholecystectomy
    - Numbers, deaths, complications
  - Colorectal resection
    - Numbers, deaths, complications

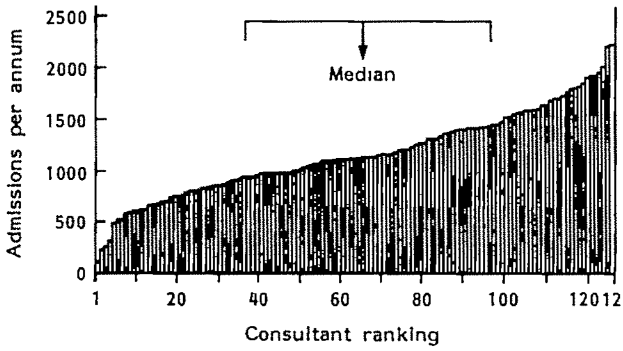

Figure 1 *Overall admissions* per annum *from data from 127 consultants The median and interquartile range are shown. Total admissions, 147 882, mean, 1164*

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Table 2 *Recommended values for use in surgical audit and surgical workload analysis*[5]

	Manpower equivalents
Consultant	1·0
Higher surgical trainee	0·75
Staff grade	
Senior registrar	
Clinical assistant	
Basic surgical trainee	0·5
Registrar	
Senior house officer	

Service equivalent value equals the total value

Table 3 *Intermediate procedures equivalents*

BUPA category	Intermediate equivalent value
Minor	0·5
Intermediate	1·0
Major	1·75
Major plus	2·2
Complex major A–D (now 1–5)	4·0*

*All complex major procedures were grouped together since there were so few in each category The value reflects the fact that all were either C or D. BUPA, British United Provident Association

A meeting was held on 6 June 1991 at which the results were presented to surgeons who had taken part in the exercise. Each of these was given a questionnaire to assess reaction to the analysis and process.

Results

Confidential numbers were requested by 220 (21 per cent) of the surgeons contacted. Of these, 160 (73 per cent) returned data on some or all of the items requested. Surgeons returned data when available; it was made clear that it was not necessary to complete the whole pro forma to participate and, therefore, variable numbers appeared in each of the analyses. The results of the workload analyses are shown in *Table 4*. The discrepancy in variable junior staff is corrected by dividing the total number of admissions per year by the service equivalent value. The complexity of operations performed is corrected by dividing the total by the intermediate equivalents value.

Some of the results of the case mix treated are shown in *Table 5* and *Figure 2*. Surgeons were given personal figures for each diagnosis (*Figure 2*) and for operative groups treated.

Details of morbidity and mortality came from 121 surgeons who returned data on deaths and/or complications covering 136 758 admissions and 119 588 operations (*Table 6*). More than 100 surgeons gave overall complication rates and 85 details of types of complications. Only 41 could break these down into major and minor complications.

Colorectal resection

A total of 2769 colonic resections were reported by 86 consultants (range 1–101 each). The mean mortality rate was 6 (range 0–43) per cent, the mean complication rate was 28 (range 0–211) per cent and the mean anastomotic leak rate 2·3 (range 0–12·5) per cent. The commonest complications were related to the abdominal wound (mean 9·8 (range 0–37) per cent). The mean hospital stay was 13·1 (range 2·3–27) days.

Table 5 *Proportion of patients treated in the lowest and highest age groups*

Patient age	No of consultants	No reported	Mean (%)
<10 years	122	7037	5 (0–13)
>60 years	122	53 707	39 (17–67)

Values in parentheses are ranges

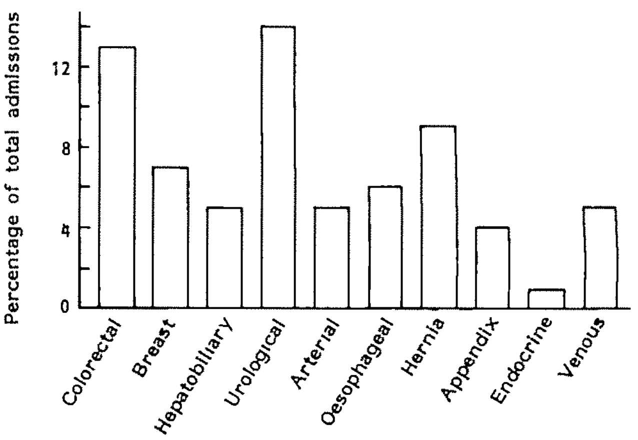

Figure 2 *Diagnostic case mix Data were requested for each of ten diagnostic groups, the rest of the admissions fell into other miscellaneous groups*

Table 4 *Resources and workload*

	No. of consultants	No. reported	Mean
Resources			
Manpower available (SEV)	111		1·58 (0·5–2·75)
Available theatre sessions per week	110		3 (1–7)
Cancelled theatre sessions per year	67		14 (0–55)
Beds available	100		19 (5–40)
Occupied beds per day	105		12 (1–29)
Workload			
Overall admissions	127	147 882	1164 (121–2216)
Overall operations	122	122 620	1005 (121–2071)
Day-case admissions	80	26 384	329 (20–937)
Non-operative admissions	114	30 529	268 (2–950)
Emergency admissions (%)	126	47 980	34 (7–71)
Admissions per SEV	111	84 232	759 (183–1673)
Intermediate equivalent value per year	97	92 241	951 (134–2271)
Intermediate equivalent value per SEV	88		626 (195–1211)
Mean stay length	105		4 (1–8)

Values in parentheses are ranges. SEV, service equivalent value

Table 6 *Overall complications per admission*

	No. of consultants	No. of complications	Mean rate per consultant (%)
Overall mortality	121	2539	2 (0–5)
Mortality after operation	121	1183	1 (0–5)
Overall complication rate	100	6101	6 (0–22)
Complications			
Wound	85	1306	1·4 (0–5·8)
Respiratory	85	1029	1·1 (0–4·2)
Haemorrhage	85	227	0·2 (0–1·1)
Cardiovascular	85	858	0·9 (0–4·2)
Gastrointestinal	85	613	0·7 (0–4·0)
Genitourinary	85	780	0·9 (0–3·7)
Metabolic	85	321	0·3 (0–2·4)
Nervous system	85	185	0·2 (0–1·3)
Miscellaneous	85	857	1·1 (0–4·1)
Complication rate after operation	48	2795	6 (1–23)
Major complications after operation	41	929	2·7 (0–8·1)
Minor complications after operation	41	1106	3·2 (0–12·2)

Values in parentheses are ranges

Table 7 *Results of survey after the meeting of surgeons contributing to the audit*

Question	No. of positive responses
Was the meeting useful?	32
Did the data surprise you?	9
Have you performed further analysis?	13
Have you changed your practice?	5
Should this exercise be repeated?	33

A total of 33 surgeons responded

Cholecystectomy

Results were returned by 126 surgeons on 4885 cholecystectomies: 3212 open (111 surgeons) and 1673 laparoscopic (47 surgeons). Of the latter, 92 (5·5 per cent) were converted to open operation. Sixteen deaths were reported after open operation (0·50 per cent) and two (0·12 per cent) after laparoscopic surgery. The morbidity rates after these two procedures were 13·9 and 7·9 per cent respectively; the morbidity rate after conversion was 9·8 per cent. The mean hospital stay after open cholecystectomy was 7·4 (range 4–16) days and after the laparoscopic operation 2·2 (range 1–5) days.

Responses to survey

Forty surgeons who supplied data and attended the meeting on 6 June 1991 were given a questionnaire and 33 responses were received. *Table 7* shows that by 2 months after the analysis of the data 39 per cent of those who returned the survey had examined the data further and 15 per cent had altered their practice as a result.

Discussion

Comparisons between the activities of different centres in the UK have been found to be of value in the past although these have often involved only studies of mortality[8,9].

With the advent of computerized surgical audit the opportunity arose for users of similar software to compare their annual results. This development was encouraged by The Royal College of Surgeons of England and the users of one such software system[10] held a meeting at the College in January 1990, followed by similar meetings[11]. Based on the success of these meetings the College established a comparative confidential audit service. The benefits of setting up such a service are that surgeons are able to compare personal results with a large database, the size of which tends to compensate for irregularities in the collection of the data. Meaningful comparisons can therefore be made. Discordant results should stimulate an examination of local practice in an attempt to explain the differences. Usually these will be explained by local variations in practice but may highlight deficiencies in surgical technique or administration.

This audit service was confidential and voluntary. Raw audit data are open to misinterpretation. For example, a hospital that has a policy of admitting patients with terminal cancer may be reflecting a caring attitude but will show a high mortality rate in audit studies. Insisting that such patients are treated at home will lower mortality rates but may not be in the interests of the local community or the patients. Such interpretations may be quoted in the popular press[12]. If surgeons are encouraged to collect and analyse data, as described in this study, it may be possible to produce some standardized mortality rates that are of value to the public. Confidentiality removes the value of producing good results simply to enhance the status of a unit, by case selection, changing discharge policies and by fabricating results. In a confidential system there is no personal benefit from these manoeuvres.

This service was designed to be voluntary. Compulsion would be a good way to ensure that a large amount of inaccurate data were included but surgeons who take part voluntarily are more likely to be interested in the result and therefore in the quality of data input.

In setting up a comparative audit service a number of compromises must be made. A complicated pro forma will be a disincentive, yet if it is too simple no useful results will be obtained. By allowing surgeons to make returns excluding some items, a larger number were encouraged to take part. Those who did take part but were unable to produce mortality and morbidity figures were stimulated to develop such systems in the future. Many were unable to participate because of lack of data systems. If the authorities encourage and recommend audit then facilities must be provided.

The overall complication and mortality rates in this and two previous studies at the College are similar[10,11]. The results of the laparoscopic cholecystectomy survey are close to those of the European[13] and North American[14] studies. These similarities encourage the view that crude audit data are not wildly inaccurate in representing current surgical practice.

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Short note

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Small bowel transit time in patients with intra-abdominal adhesions

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Intra-abdominal adhesions occur in over 90 per cent of patients following laparotomy[1]. Because adhesions cause considerable problems to both patients and surgeons[2], much research has centred on methods to prevent their formation The success of these methods is difficult to assess because repeat laparotomy is uncommon, and thus the only clearly defined clinical endpoint is the long-term incidence of adhesional bowel obstruction The aim of this study was to measure small bowel transit time in patients with intra-abdominal adhesions and thus to determine the possible role of this technique in identifying patients with small bowel adhesions.

Patients and methods

Fifteen patients were selected who had undergone operation within the past 3 years for extensive adhesional disease without significant (>20 cm) resection of small bowel and with no history of gastrectomy or vagotomy The operations preceding the development of adhesional disease were appendicectomy (seven patients), hysterectomy (three), oversewing of perforated peptic ulcer (two), caesarean section (two) and cholecystectomy (one). Another 15 patients, matched for age and sex, who had never suffered peritonitis or undergone laparotomy, were selected as controls.

None of the 30 patients had evidence of any other gastrointestinal disease, and none was receiving any medication affecting bowel transit time. None suffered from any serious concomitant disease All the patients with adhesions were asymptomatic at the time of analysis The study was granted approval by the hospital ethical committee, and all 30 patients gave informed consent

The orocaecal transit time was measured using the lactulose hydrogen breath test. After an overnight fast, the patient ingested a standard lactulose meal (40 g glucose, 15 g Casilan (Crookes Healthcare, Nottingham, UK), 18 g corn oil, made up to 270 ml with water to which was added 30 g lactulose)[3] and provided end expiratory breath samples at intervals of 10 min The breath hydrogen concentration was measured using a dedicated electrochemical cell (EC60; Bedfont Technical Instruments, Sittingbourne, Kent, UK). The orocaecal transit time was recorded as the time after ingestion at which there was a sustained rise in expired breath hydrogen 10 p.p.m. above the fasting level[3].

Results

Two control patients and one with adhesions did not produce hydrogen. The orocaecal transit time was prolonged in the adhesion group compared with the control group (median 140 *versus* 110 min, $P < 0{\cdot}05$; Mann–Whitney U test) (*Figure 1*).

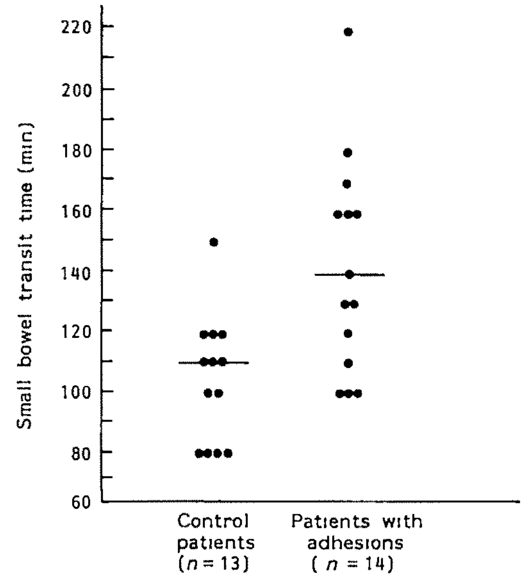

Figure 1 *Orocaecal transit time in patients with adhesions and in controls. Bars are median values*

Discussion

The lactulose hydrogen breath test provides a simple non-invasive estimate of small bowel transit time[4] and is considered to be a useful research tool for this purpose[5]. Intrasubject variability is reduced by the administration of lactulose in the form of a semiliquid meal[3].

The results of this study suggest that transit in patients with intra-abdominal adhesions may be delayed in the absence of symptoms or clinical evidence of obstruction. The observed overlap in transit time between the two groups shows that the test is not specific for intra-abdominal adhesions. Follow-up studies will be required to determine whether those patients with a more marked prolongation of transit time will prove to be at greater risk of developing clinical symptoms. In addition, the lactulose hydrogen breath test may prove useful in the assessment of methods designed to prevent formation of intra-abdominal adhesions

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Presentation of abdominal tuberculosis to general surgeons

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Abdominal tuberculosis (TB) continues to give rise to diagnostic and therapeutic challenges. A total of 24 patients with abdominal TB who presented to general surgeons over a 9-year period have been reviewed. Most (92 per cent) of these patients were Asian; only one had a past history of pulmonary TB. The most common presenting complaint was abdominal pain in 21 patients (88 per cent) with the associated symptoms of weight loss in 18 (75 per cent), anorexia in 15 (62 per cent) and night sweats in 13 (54 per cent). A tissue diagnosis was obtained in 18 patients (75 per cent) and 17 patients (71 per cent) underwent laparotomy. These results show that the diagnosis of abdominal TB is still difficult to establish, and that many patients undergo laparotomy despite the existence of less invasive diagnostic procedures.

The incidence of abdominal tuberculosis (TB) is increasing in the UK[1]. This is due to the large Asian immigrant population, a group in which abdominal TB should always be considered in the differential diagnosis of abdominal pain. However, the diagnosis of abdominal TB can often be difficult to establish because the disease may present with a wide variety of non-specific symptoms and signs. In addition, the pattern of disease is changing, and many patients with abdominal TB do not have the associated pulmonary disease that may aid diagnosis[2]. A high index of suspicion is therefore required to make a prompt diagnosis; failure to do so may lead to unnecessary morbidity and mortality because of the consequent delay in treatment.

Twenty-four patients with abdominal TB who presented to general surgeons in Leicester have been reviewed retrospectively to document the clinical features and methods used to establish the diagnosis of this disease.

Patients and methods

The case notes of 24 patients later found to have abdominal TB were reviewed. All were referred by their general practitioners to general surgeons in Leicester during the period 1981–1989. Seven patients (29 per cent) were admitted as emergencies and 17 (71 per cent) initially seen as outpatients. Patients seen in surgical outpatient clinics once a diagnosis of abdominal TB had already been made were excluded from the study.

The mean age of patients was 31 (range 9–71) years; 12 were male. Most patients were Asian (22 patients, 92 per cent) and two (8 per cent) were Caucasian. One patient had a history of pulmonary TB and four a family history of TB.

Results

Presenting symptoms

Abdominal pain was the most common indication for referral and the primary complaint in 21 patients (88 per cent). Two patients (8 per cent) were referred with abdominal distension and one (4 per cent) with unexplained weight loss (*Figure 1*). The most common site of abdominal pain was the right iliac fossa (11 patients; 52 per cent) (*Figure 2*). Associated symptoms included weight loss in 18 patients (75 per cent), anorexia in 15 (62 per cent) and night sweats in 13 (54 per cent). Vomiting was present in six patients (25 per cent) and diarrhoea in one (4 per cent).

The mean duration of symptoms before presentation to hospital was 2·2 months (range 3 days to 8 months).

Clinical examination

The abnormalities most frequently encountered on physical examination were pyrexia in 15 patients (62 per cent) and ascites in ten (42 per cent). Nine patients (38 per cent) had an abdominal mass, eight in the right iliac fossa. Seven patients (29 per cent) had abdominal tenderness, which was maximal in the right iliac fossa in four.

Investigations

The mean haemoglobin concentration was 11·6 (range 9·4–15·0) g/dl; microcytic indices were found in 18 patients (75 per cent). The white cell count was raised ($>11 \times 10^9$/l) in six patients (25 per cent). The erythrocyte sedimentation rate (ESR) was measured in nine patients (38 per cent) and

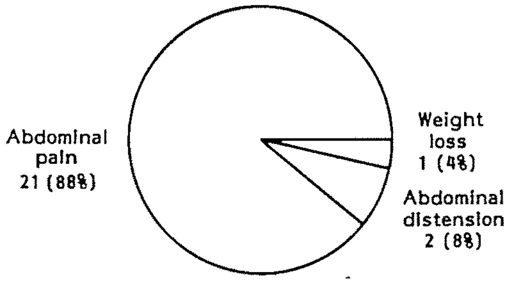

Figure 1 *Indications for referral of 24 patients with abdominal tuberculosis*

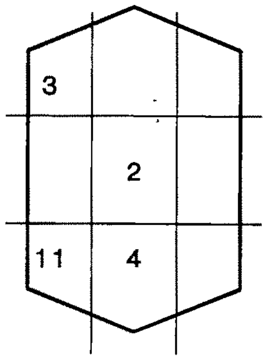

Figure 2 *Schematic representation of the abdomen showing site of pain in 21 patients with abdominal tuberculosis. Pain was generalized in one patient*

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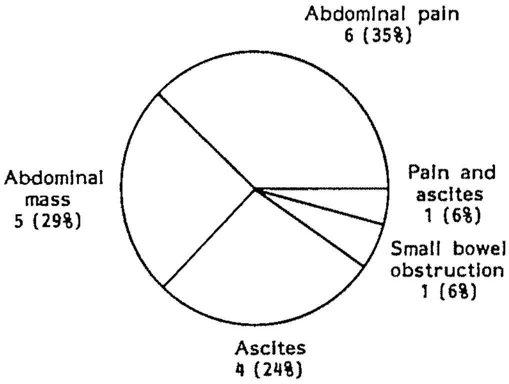

Figure 3 *Indications for laparotomy in 17 patients with abdominal tuberculosis*

all values were abnormally high. A Mantoux test was performed in 14 patients (58 per cent) and was positive in ten (71 per cent).

Radiology. Chest radiography was performed on 23 patients (96 per cent); only two of these were abnormal, showing healed pulmonary TB. Ten patients (42 per cent) underwent plain abdominal radiography: six were normal, two revealed ascites and two showed small bowel obstruction Eight patients (33 per cent) were subjected to barium enema, of whom six showed an abnormal caecum. Barium meal and follow-through was performed on three patients and all demonstrated caecal abnormalities. Eleven patients (46 per cent) underwent abdominal ultrasonography; seven sonograms showed ascites, including one that showed ascites with interlacing septa crossing the peritoneal cavity. A mass in the right iliac fossa was seen in two patients.

Diagnosis

The final diagnosis was tuberculous peritonitis in 16 patients (67 per cent) and TB of the gastrointestinal tract in eight (33 per cent), including seven with ileocaecal TB and one with jejunal TB.

Diagnosis of TB was made by histological examination of tissue in 18 patients (75 per cent), obtained at laparotomy in 17 and by laparoscopic biopsy in one Three patients who had had a laparotomy had also undergone attempted laparoscopy which failed. Two patients underwent colonoscopy in one this failed to reach the caecum and in the other caecal biopsies showed non-specific histological changes. Six patients (25 per cent) did not have their diagnosis of TB proven histologically

The indications for laparotomy are shown in *Figure 3.* The most frequent indication was abdominal pain alone (six patients). four of these had a lymph node biopsy, one a jejunal resection and one an appendicectomy for appendicitis caused by surrounding lymph node compression. Five patients underwent laparotomy for an abdominal mass, of which four were in the right iliac fossa: two of these patients underwent right hemicolectomy and the other two a mesenteric lymph node biopsy. The fifth patient with an abdominal mass underwent division of small bowel adhesions and lymph node biopsy. One patient underwent laparotomy, division of adhesions for small bowel obstruction, and lymph node biopsy. Four patients were operated on with ascites and all had mesenteric node biopsies One patient had a combination of abdominal pain and ascites and underwent lymph node biopsy.

Histology and microbiology

Tissue was obtained from 18 patients (75 per cent); ten had a positive diagnosis of TB made either by identification or culture of acid-fast bacilli, or the presence of caseating granulomas on histological examination. In the remaining eight patients from whom tissue was obtained, acid-fast bacilli were not isolated and caseating granulomas not seen. However, all had non-caseating granulomas, the histological features of which were highly suggestive of TB Combined with the clinical findings and investigations, these appearances made TB highly probable, a diagnosis that was substantiated by a dramatic response to antituberculous chemotherapy. A similar response to chemotherapy was seen in the six patients in whom the diagnosis of TB was made on clinical grounds without histological or microbiological evidence.

Discussion

Abdominal TB is a disease with a worldwide distribution which is increasing in incidence in the UK mainly as a result of the arrival of Asian immigrants[1]. Despite its increasing frequency, there have been few reported series documenting the features of the disease in the UK[2–6] and many surgeons still believe that it is uncommon. This fallacy may lead to missed diagnosis and delayed treatment. A recent study[3] from a west London district general hospital serving a large Asian community found that abdominal TB was diagnosed in 90 patients presenting to various specialties over a 10-year period. During the same period, Crohn's disease was diagnosed in 102 patients admitted to the same hospital Abdominal TB must therefore be considered as a possible diagnosis in any Asian patient presenting with acute or chronic abdominal pain. Furthermore, although abdominal and pulmonary TB frequently coexist in developing countries[7–9], they are not usually associated in the UK[2], and the absence of pulmonary pathology does not exclude the diagnosis of intra-abdominal disease. Indeed, only one of the patients in this study admitted to a medical history of pulmonary TB, and only two had radiological evidence of previous pulmonary disease. A previous comprehensive study of over 1000 collected cases[10] showed that abdominal TB is predominantly a disease of young females, but 50 per cent of the patients reported here were male.

Although abdominal TB may present with a variety of non-specific abdominal symptoms and signs, the most common primary complaint is abdominal pain[11,12], this was the primary reason for referral in 88 per cent of patients in the present study. The most frequent site of pain was the right iliac fossa (52 per cent), but other authors[11] have found it to be most frequently umbilical (35 per cent) or generalized (32 per cent), and localized to the right iliac fossa in only 21 per cent The presence of associated symptoms is also common[12–14], with weight loss occurring in 75 per cent, anorexia in 62 per cent, and night sweats in 54 per cent of patients in this study. The mean duration of symptoms has been reported by different authors[15] to be 4·7 months, twice as long as that (2·2 months) in this series.

On examination, the most common abdominal finding is usually ascites secondary to peritoneal disease[14], present in 42 per cent of patients reported here. Abdominal tenderness was elicited in only 29 per cent of patients, whereas other studies have found it to occur in as many as two-thirds[10]. The presence of an abdominal mass, especially in the right iliac fossa, is another common finding and occurred in 38 per cent of patients in the present study. It may be caused by a hypertrophic ileocaecal lesion, a mass of lymph nodes, adherent omentum, or loculated ascites[11,13,14,16].

Haematological and immunological tests commonly show non-specific changes. A mean haemoglobin level of <12 g/dl has been reported in 80 per cent of cases[11], along with a raised white cell count in 32 per cent[17] and a raised ESR in over 90 per cent[11] Skin tests (Heaf, Mantoux) are positive in over 70 per cent of patients[15]. The findings reported in this paper are consistent with these observations.

Abdominal radiography may show dilated loops of bowel, fluid levels, calcified lymph nodes and ascites. In the patients in this report contrast studies usually showed a caecal abnormality It may be difficult to differentiate between TB and Crohn's disease or carcinoma on barium films alone, and abdominal ultrasonography or colonoscopy may then be useful

A definitive diagnosis of TB can be made only if caseation is demonstrated on histological examination, or if acid-fast bacilli are demonstrated in the tissue by Ziehl–Nielsen staining, culture, or guinea-pig inoculation. Caseation is often not seen in patients from the Indian subcontinent, but in cases of non-caseating TB the granulomas are numerous, large, well defined and may coalesce. Acid-fast bacilli may not be demonstrated, even though the lesions are histologically typical of tuberculosis[1,18].

A therapeutic trial of antituberculous chemotherapy is often justified in Asian patients with abdominal symptoms and signs that are suggestive of TB without histological confirmation. The diagnosis is confirmed by a rapid response to treatment. It is important to monitor the patient's progress because healing of the inflammatory process by fibrosis may lead to intestinal obstruction.

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An improved means of faecal diversion: the trephine stoma

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Twenty-four patients in whom trephine stoma formation was performed over a 4-year period are described. This procedure permits the formation of an end ileostomy or colostomy without laparotomy. It is simple, rapid, safe and allows speedy recovery. It is widely applicable and previous abdominal surgery is no contraindication. The procedure was impossible in two patients who required laparotomy and in a third in whom a loop colostomy was created. Operation time was shorter and postoperative opiate requirements less than when laparotomy was undertaken for stoma formation. Follow-up (median 1 year) of 17 patients confirmed a low incidence of complications (two prolapses, one parastomal hernia) after trephine stoma formation. This procedure is recommended as the preferred method of ileostomy or colostomy formation when laparotomy is not otherwise indicated.

The formation of a colostomy or ileostomy may be required in the treatment of patients with faecal incontinence, recurrent pelvic malignancy and in certain other functional colorectal disorders. End stomas offer more complete faecal diversion[1] and are considerably easier to manage than bulky loop stomas, but while the latter can be constructed locally, the formation of an end stoma has traditionally required laparotomy. When there is no therapeutic need for this, the laparotomy merely increases the magnitude of operation to be endured by the patient. A means of performing end colostomy and end ileostomy is described in which the operation is performed through the trephine hole through which the bowel will ultimately be brought to form the stoma. The results of this 'trephine stoma' technique have been compared with those in patients undergoing laparotomy and stoma formation during the same period.

Patients and methods

Patients

Twenty-four patients (19 women, five men) of median age 49 (range 24–79) years underwent successful end stoma formation without laparotomy between February 1988 and December 1991. In 22 of these patients an end sigmoid colostomy was constructed and an ileostomy was fashioned in two. In a further three patients an attempt at trephine colostomy formation was not successful. The indications for surgery are shown in *Table 1*.

Previous abdominal surgery had been performed in 16 patients, previous left colonic surgery in six and previous radiotherapy to the pelvis in six. Three patients had an ileal urostomy in place. Patients without advanced malignant disease were followed after discharge to monitor complications.

Ten patients underwent laparotomy for stoma formation during this time. The age of this group ranged from 18 to 69 (median 44) years, two were men. Incontinence (six patients) was again the main indication for stoma formation; two patients had severe constipation and abdominal pain, one required loop transverse colostomy formation and one had an obstructing rectal carcinoma. Nine of these ten patients had undergone abdominal surgery previously. Patients were selected for laparotomy or trephine stoma on the preference of the surgeon and some selection bias must therefore exist.

Patients undergoing laparotomy were compared with those undergoing the trephine stoma procedure with respect to length of hospital stay, operation time and opiate administration. Two patients who underwent laparotomy after failed trephine colostomy and one undergoing simultaneous dismantling of an ileorectal anastomosis were excluded from the analysis of the length of operation. Patients having a trephine colostomy with concurrent disease or undergoing other procedures simultaneously were similarly excluded. A consultant surgeon performed (or assisted in) 13 (four) of 24 successful trephine colostomy operations and five (one) of ten colostomy with laparotomy procedures.

The ideal site for the stoma was usually marked before operation by a stoma therapist. All patients received antibiotic prophylaxis with cefuroxime 1·5 g and metronidazole 1·5 g on induction of anaesthesia. Sodium picosulphate was used to effect bowel preparation in patients undergoing stoma formation for functional disorders.

Colostomy formation

Immediately before the procedure a 20-Fr Foley or similar catheter was placed in the rectum and connected to the bellows from a sigmoidoscope. The patient was then usually placed supine, although the Lloyd-Davies position was adopted if necessary for sigmoidoscopy or any simultaneous procedure. A standard colostomy trephine opening was made in the usual way at the premarked site, usually through the lateral half of the rectus abdominis muscle. After splitting the muscle, the posterior sheath and peritoneum were lifted with an artery forceps and the peritoneal cavity entered. Langenbeck retractors were used to displace the wound inferolaterally. The typical features of the sigmoid colon allowed its positive identification. It was then delivered into the wound and held with an encircling rubber tube. It was necessary to mobilize the sigmoid colon in only three of 24 cases. A soft clamp was placed across the bowel and air insufflated into the rectum through the previously positioned catheter. The distension of the sigmoid on one side of the clamp identified this as the distal end of the colon. The sigmoid mesocolon was divided for 4 cm and the bowel divided after closing the distal colon with a TA55 stapler (Auto Suture, Ascot, UK). The closed distal colon was replaced within the peritoneal cavity and the proximal end sutured to the wound in the usual fashion. Oral intake, initially with liquids, was resumed immediately.

Ileostomy formation

Through a trephine in the right iliac fossa, the small bowel was delivered and traced distally to the ileocaecal junction. Identification of the caecum confirmed the correct site for stoma formation, a few

Table 1 *Indications for end stoma formation without laparotomy in 24 patients*

Sigmoid colostomy	
Faecal incontinence	13
Recurrent malignant rectal fistula	4
To allow perianal skin graft or reconstruction	3
Stenosis after anterior resection	1
Solitary rectal ulcer syndrome	1
Ileostomy	
Abdominal pain	1
Constipation	1

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centimetres proximally. Again, the mesentery was divided for a short distance only and the distal bowel was closed and returned to the abdominal cavity before the ileostomy was created in the usual way.

Results

Trephine stoma formation was attempted in 27 patients and completed successfully in 24. Only two patients required laparotomy: the first failure occurred in a woman with a previous left hemicolectomy and the second in a patient who had undergone colostomy and then a pull-through procedure for imperforate anus. In a third patient with a malignant rectovesical fistula, the bowel was successfully delivered but the tumour prevented identification of the distal limb. A sigmoid loop colostomy was therefore created.

There were no postoperative deaths and only two complications within 30 days of stoma formation: one patient developed pyrexia and abdominal pain on the day after trephine ileostomy which settled within 24 h; a second required early resiting of the stoma because a skinfold prevented easy fitting of the bag.

Trephine stoma formation was accomplished rapidly and patient recovery was speedy. Opiate analgesia was required for a median of only five doses. Operating time and opiate requirements were less than for the patients who underwent laparotomy for stoma formation (*Table 2*).

A total of 17 patients with benign disease have been followed for a median of 1 year (range 2–48 months) after trephine stoma formation. Two stomas have required refashioning for prolapse and in one of these a parastomal hernia was repaired at the same procedure. One ileostomy has been closed without complication. One elderly woman developed an asymptomatic parastomal hernia 18 months after surgery and died from unrelated causes 1 year later.

Table 2 *Details of 14 patients undergoing trephine stoma formation and seven undergoing stoma formation by laparotomy without concurrent disease*

	Trephine stoma (n = 14)	Laparotomy and stoma (n = 7)
Operation time (min)	35 (10–65)	60 (45–120)
Opiates		
Doses (no.)	5 (1–9)	13 (7–25)
Duration (h)	32 (4–58)	70 (44–138)
Hospital stay (days)	9 (4–21)	12 (11–13)

Values are median (range)

Discussion

This study shows that the trephine stoma procedure is a safe and successful method of creating an end ileostomy or colostomy without laparotomy. The operation is widely applicable and causes little physical insult to the patient. Senapati and Phillips[2] noted the pitfalls of trephine colostomy to be difficulty in the identification and confirmation of the orientation of the sigmoid colon. The insufflation technique described in the present paper makes it easy to distinguish the proximal and distal limbs of the sigmoid colon. In patients with recurrent pelvic malignancy with rectovaginal fistula, a narrow catheter can usually be inserted past the tumour. In only one such case did recurrent disease prevent identification of the proximal bowel with certainty; a sigmoid loop colostomy was created. Previous surgery to the left colon is no contraindication to the procedure although difficulty may occasionally be encountered, as evidenced by the two failed procedures. Senapati and Phillips reported a similar failure rate[2].

Follow-up of the patients undergoing trephine stoma formation has shown a low complication rate, and failure to close the lateral space has caused no problems. In contrast to the previous report[2], no stomal retraction has occurred, although two prolapses were observed. Local stoma closure should present no difficulty as the bowel ends remain joined by the mesentery.

Because of differences in patient selection, conclusions can be drawn from the comparison with laparotomy only with care, but the trephine stoma appears to be a much less traumatic procedure. The lack of difference in length of hospitalization is not surprising as much of the postoperative stay is spent learning care of the stoma.

It is of considerable advantage to the patient that the initial learning of stoma care can be accomplished without pain from, or fear of contamination of, a laparotomy wound. The small end stoma is considerably easier to care for than a bulky loop stoma and known to provide more complete faecal diversion[1].

Trephine stoma formation is proving a popular and successful method of achieving total defunction of the bowel. The technique is simple and holds several advantages over alternative procedures. It is to be commended.

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Role of the rectum in the physiological and clinical results of coloanal and colorectal anastomosis after anterior resection for rectal carcinoma

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This study investigated the relationships between length of residual anorectum, anorectal physiological function and clinical outcome after anterior resection for rectal carcinoma. Thirty-four patients were studied a median of 13 (range 4–100) months after anterior resection. They were compared with a control group of ten patients who had undergone sigmoid colectomy for carcinoma without rectal excision. Resting anal pressure was found to be lower after coloanal than after colorectal anastomosis, and the capacity of the (neo)rectum was less after coloanal than after colorectal anastomosis. The (neo)rectoanal inhibitory reflex was found to be present in each patient, but maximum anal pressure during this 'sampling' reflex was significantly lower ($P < 0{\cdot}01$) after coloanal than after colorectal anastomosis, and the volume required for maximal inhibition of the sphincter was also less ($P < 0{\cdot}01$). At 1 year after operation, median bowel frequency was greater after coloanal (4 per day) than after colorectal (2 per day) anastomosis and the degree of urgency of defaecation was also greater ($P < 0{\cdot}01$). Quality of life in terms of anorectal function after anterior resection is thus significantly influenced by the length of rectum that is left. This, in turn, influences the functional capacity of the neorectum and the degree of inhibition of the anal sphincter during the neorectoanal inhibitory reflex.

Most patients who undergo potentially curative resection for rectal cancer now have the anal sphincter preserved and intestinal continuity restored by means of low anterior resection. The need to cure the cancer by obtaining distal radical clearance of rectum and mesorectum means that most patients presenting with tumours of the lower two-thirds of the rectum will have either coloanal or very low colorectal anastomosis, whereas those with tumours situated in the upper rectum will usually undergo colorectal anastomosis with preservation of a few centimetres of distal rectum. Some surgeons go further and advocate radical excision of the rectum and entire mesorectum in most patients with rectal cancer[1].

The quality of life of patients after such sphincter-saving surgery is undoubtedly better than that after abdominoperineal excision of the rectum with a permanent colostomy[2]. Furthermore, recurrence of tumour is no more common and survival (stage for stage) as good after anterior resection as after abdominoperineal excision[3] However, 25–50 per cent of patients experience problems with anorectal function after operation, complaining in particular of urgency of defaecation and of minor faecal leakage[4] Such problems are at their worst in the early months after operation, but may persist.

The aim of this study was to investigate the relationships between clinical functional outcome after low anterior resection, length of residual rectum and anorectal physiological function as measured by manometry. The hypothesis was that the functional outcome might be related to the length of residual rectum, and that preservation of some distal rectum, if permissible in terms of cancer cure, may lead to a better quality of life than that achieved by complete excision of the rectum followed by coloanal anastomosis.

Patients and methods

A total of 34 patients were studied, each of whom had undergone potentially curative anterior resection for rectal carcinoma between 1983 and 1990 The height of the anastomosis above the anal verge (*A* cm) was determined with a rigid sigmoidoscope, the length of the anal high-pressure zone (HPZ) (*B* cm) by anorectal manometry, and the length of residual rectum calculated by subtracting *B* from *A* Three groups of patients were defined, with similar ages and durations of follow-up after operation, but with different lengths of residual rectum (0, <4 and ≥4 cm). A control group of ten patients was also studied: each had undergone sigmoid colectomy for carcinoma, but the rectum had been left intact (*Table 1*) None of the patients had evidence of recurrent carcinoma and none had received radiotherapy.

Each patient underwent laboratory studies of anal sphincter function a median of 13 (range 4–100) months after operation. Anal pressure was measured by the station pull-through technique as described previously[5] The capacity of the (neo)rectum was measured by placing a balloon with its lower extremity 10 cm from the anal verge, and inflating it with air at a rate of 1 ml s^{-1} until the patient experienced either discomfort or a strong desire to defaecate. The (neo)rectoanal inhibitory reflex was assessed by measuring the response of the entire length of the anal sphincter to distension of the (neo)rectum; a 20 per cent decrease in sphincter pressure denoted a positive reflex[6]. Sensation was tested by measuring threshold electrosensitivity of the anal mucosa using a bipolar, constant-current stimulator probe lubricated with a solution of KY jelly (propylene glycol, glycerol hydroxyethylcellulose and sodium phosphate in water; Johnson and Johnson, Ascot, UK) and normal saline in equal volumes[7].

Anal continence was assessed clinically by two doctors who had not been part of the surgical team that performed the operation They questioned each patient about bowel frequency, ability to defer defaecation, anal soreness and faecal leakage This information was correlated with responses to a quality-of-life questionnaire that was completed by the patients in their own time Significant faecal leakage

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Table 1 *Characteristics of patients and clinical results*

	Coloanal anastomosis	Colorectal anastomosis		
		<4 cm	≥4 cm	>12 cm
No. of patients	11	12	11	10
Median age (years)	65 (58–61)	69 (43–77)	66 (43–81)	68 (48–79)
Sex ratio (M:F)	5:6	7:5	5:6	4:6
Median follow-up (months)	11 (4–100)	17 (5–76)	13 (4–36)	27 (9–54)
Median height of anastomosis above HPZ (cm)	0 (0–2)	3·5 (3–4)	5 (4·5–6)	>12
Median bowel frequency per 24 h	4 (2–8)	3 (1–10)	2 (1–4)	1 (1–4)*
Urgency (*n*)	5	4	0†	0†
Faecal leakage (*n*)	8	8	2	0*

Values in parentheses are ranges. HPZ, anal canal high-pressure zone *$P < 0·01$, †$P < 0·02$ (*versus* coloanal and <4 cm, Fisher's exact test)

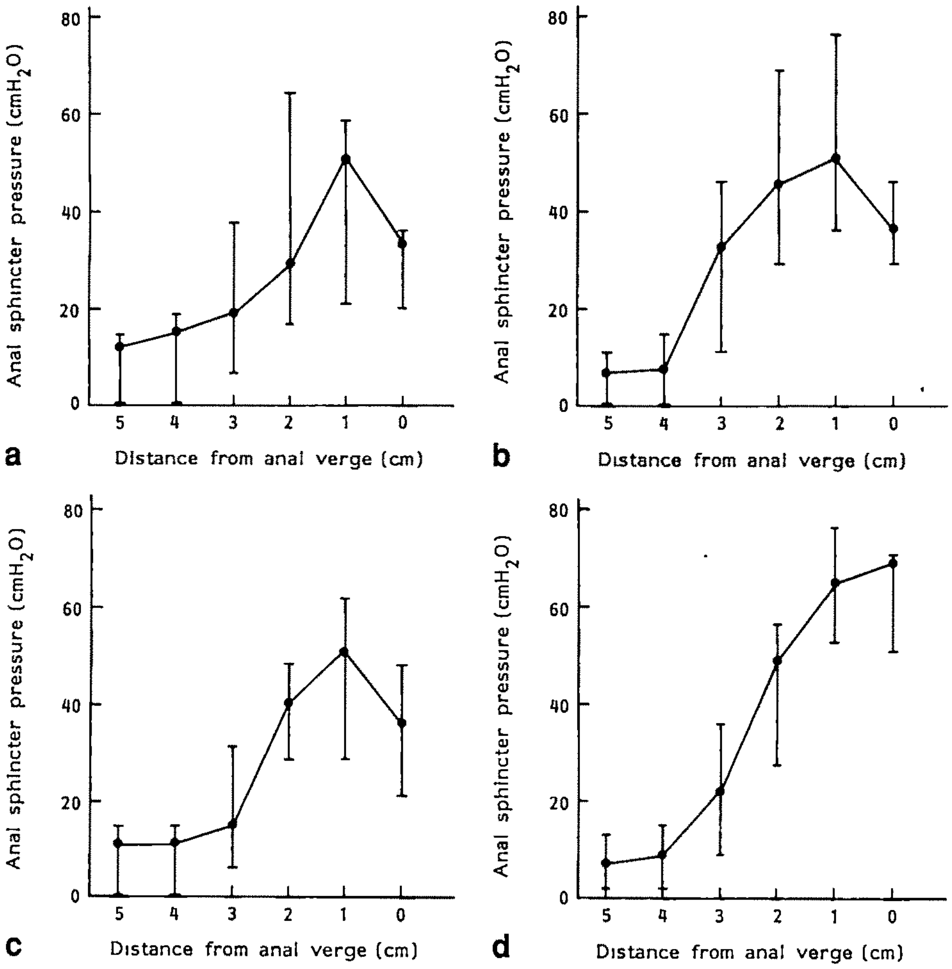

Figure 1 *Median (interquartile range) anal sphincter pressure profiles of patients with* **a** *coloanal anastomosis,* **b** *low colorectal (<4 cm) anastomosis,* **c** *colorectal (≥4 cm) anastomosis and* **d** *colorectal anastomosis (intact rectum)*

was defined arbitrarily as that occurring at least once per week, and urgency as the inability to defer defaecation for >15 min. Each patient underwent rigid sigmoidoscopy, performed by a different surgeon (B.M.S.) than the one who carried out the physiological assessment. The surgeon who performed the manometry (W.G.L.) was not aware of the level of the anastomosis above the anal verge at the time of the physiological assessment.

All grouped data are expressed as median (range). Groups were compared by Kruskal–Wallis analysis of variance and the Mann–Whitney *U* test for unpaired data. Nominal data were analysed using Fisher's exact test[8].

Results

Laboratory tests

Median maximum resting anal pressure was 51 (range 11–102) cmH_2O in the coloanal group, 66 (range 36–128) cmH_2O in patients with <4 cm and 61 (range 27–91) cmH_2O in those with ≥4 cm of residual rectum, and 69 (range 55–107) cmH_2O in the group with an intact rectum. There were no statistically significant differences between the groups. The median maximum squeeze pressure was 109 (range 55–240) cmH_2O in the coloanal group, 133 (range 58–255) cmH_2O in patients with <4 cm and 111 (range 51–189) cmH_2O in those with ≥4 cm of residual rectum, and 120 (range 65–225) cmH_2O in the group with an intact rectum. Again there were no statistically significant differences between the groups.

The pressure profiles of the anal sphincter in each group of patients are shown in *Figure 1*. Although the HPZ appeared shorter with a lower peak pressure in patients with a coloanal anastomosis than in any of the other three groups, the difference was not statistically significant.

The thresholds for sensation in the anal canal did not differ significantly between any pair of groups as determined by threshold electrosensitivity in the upper, mid and lower anal canal.

Median maximum tolerated volume is shown in *Figure 2*. Kruskal–Wallis analysis showed significant differences ($P < 0\cdot01$). Patients with coloanal anastomosis had significantly lower neorectal capacity than those with ≥4 cm of residual rectum ($P < 0\cdot01$). The control group with an intact rectum had greater rectal capacity ($P < 0\cdot01$) than any of the patients who had undergone anterior resection.

A (neo)rectoanal inhibitory reflex was present in all patients. The change in the pressure profile of the anal sphincter during distension of the (neo)rectum is shown in *Figure 3*. The pressure during (neo)rectal distension was lower than resting pressure throughout the length of the anal sphincter, but in particular in the upper part of the sphincter 3 and 2 cm from the anal verge. The absolute pressures measured in the lower 3 cm of anal canal during distension of the neorectum in patients after coloanal anastomosis were significantly lower than the absolute pressures measured in those with an intact rectum (Kruskal–

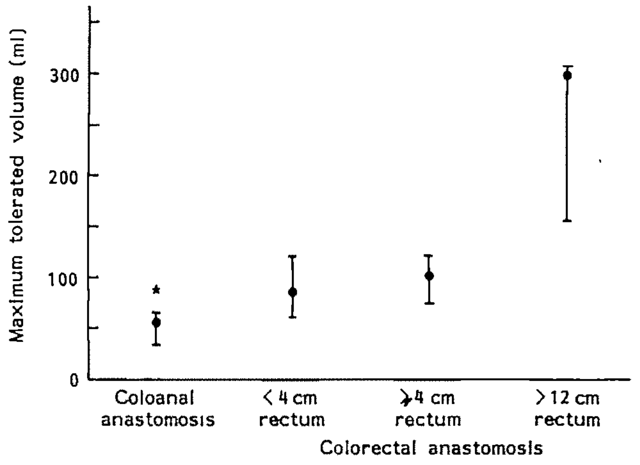

Figure 2 *Median (interquartile range) maximum tolerated volume within the (neo)rectum.* *$P < 0\cdot05$ (*coloanal* versus *≥4 cm and >12 cm, Mann–Whitney* U *test*)

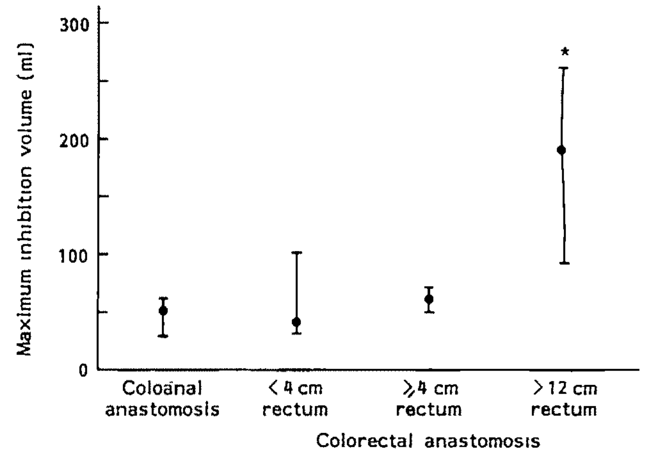

Figure 4 *Median (interquartile range) volume required to produce maximum inhibition of the anal sphincter.* *$P < 0\cdot05$ (*> 12 cm* versus *others, Mann–Whitney* U *test*)

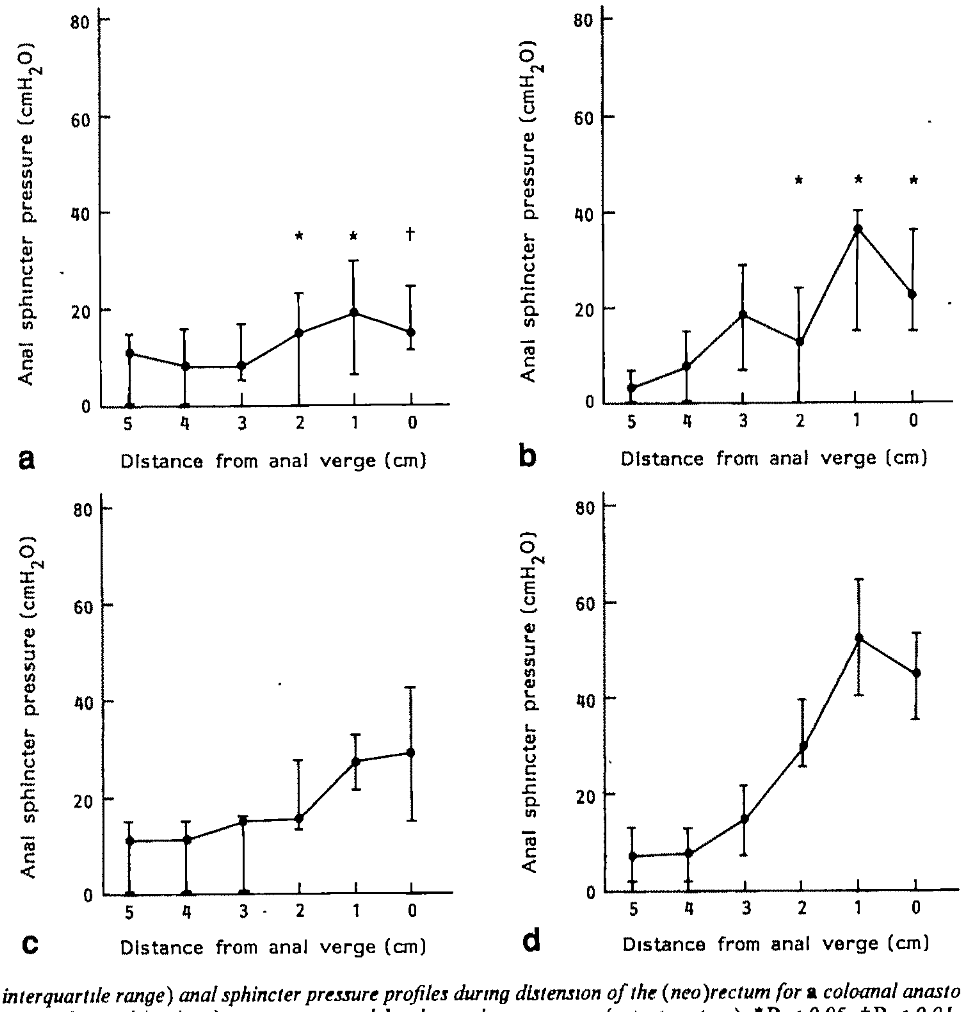

Figure 3 *Median (interquartile range) anal sphincter pressure profiles during distension of the (neo)rectum for* **a** *coloanal anastomosis,* **b** *low colorectal (< 4 cm) anastomosis,* **c** *colorectal (≥4 cm) anastomosis and* **d** *colorectal anastomosis (intact rectum).* *$P < 0\cdot05$, †$P < 0\cdot01$ (versus *pressures in* **d**, *Mann–Whitney* U *test*)

Wallis analysis: $P < 0.01$; Mann–Whitney U test: $P < 0.05$ at 2 cm, $P < 0.05$ at 1 cm, and $P < 0.01$ at 0 cm from the anal verge).

The amount of distension of the (neo)rectum required to produce maximal inhibition of the anal sphincter was significantly greater in patients with an intact rectum than in any of the other groups ($P < 0.01$, *Figure 4*).

Clinical tests

The greater the length of residual rectum, the better were the overall clinical results (*Table 1*). For example, at a median period of 1 year after operation, 24-h bowel frequency was greater in patients who had undergone coloanal or low colorectal anastomosis than in those with an intact rectum ($P < 0.01$). Urgency of defaecation was greater after coloanal or low colorectal anastomosis than in the other two groups ($P < 0.02$). Eight of 11 patients in the coloanal anastomosis group and eight of 12 undergoing low colorectal anastomosis suffered from minor faecal leakage at least once a week, whereas none of the ten patients with an intact rectum experienced faecal leakage ($P < 0.01$).

Discussion

The development and increasing use of anal sphincter-preserving surgery for rectal cancer means that most patients can now avoid a permanent colostomy, with obvious benefit to their quality of life. Moreover, local recurrence and 5-year survival rates are as good after anterior resection as after abdominoperineal resection of the rectum[3]. As a consequence of more frequent preservation of the anal sphincter in patients with rectal cancer, attention has focused on the specialized functions of the rectum.

Although the rectum acts primarily as a reservoir, fine control of defaecation results from close integration of rectal and anal function, as shown by the rectoanal inhibitory reflex: entry of a faecal bolus into the lower rectum produces reflex inhibition of the anal sphincter, which is graduated in such a way as to permit pressure in the rectum and upper anal canal to become equal, while inhibition of the more distal part of the sphincter near the anal margin is absent or less marked. This is known as 'sampling' and is thought to be central to mechanisms of continence. The present hypothesis was that preservation of as much rectal structure and function as possible would benefit the patient, provided that cancer cure and local recurrence were not thereby compromised.

The site and stage of the presenting tumour clearly determine the extent of the surgical resection required. Hence, for carcinoma of the lower third of the rectum, sacrifice of the entire rectum and mesorectum is necessary and cannot be avoided[1]. In carcinoma of the upper third of rectum or rectosigmoid, some distal rectum should always be preserved. The treatment of carcinomas of the middle third remains debatable: it is not clear whether it is better to excise the entire rectum and mesorectum or to attempt to preserve some of the distal rectum on the assumption that this will result in improved reservoir function and better integration of rectal and anal function.

It is widely assumed that good anal continence will be preserved after rectal excision for carcinoma provided that the internal anal sphincter and skeletal musculature of the pelvic floor remain intact[9]. This belief persists despite the fact that bowel frequency and urgency with minor faecal leakage are well recognized after anterior resection. These symptoms are often dismissed as a temporary nuisance that will resolve gradually in the course of the first year after operation. However, we have found that this does not always happen. The 34 patients who had undergone anterior resection were reviewed a median of 1 year after operation, yet 18 still complained of at least minor faecal leakage, and nine of these also experienced some degree of urgency. Six patients were assessed <6 months after surgery, but analysis of the data from patients 12 months or more from the time of surgery did not alter the overall results or conclusions. In our experience, if a patient is incontinent 6 months after operation, and physiological assessment demonstrates marked sphincter inhibition on neorectal distension, then improvement in function is unlikely. Sixteen patients had good anal continence, which suggests that coordinated activity of the neorectum and anus may return in many patients after anterior resection.

Resting anal pressure, which is mainly a function of the internal anal sphincter, was lower after coloanal anastomosis than in the other three groups of patients, as has been reported by others[10]. In patients with a very low colorectal anastomosis, maximum resting anal pressure was not significantly lower than in either of the two groups with higher colorectal anastomoses, while the clinical results after coloanal and very low colorectal anastomosis were similar. Maximum squeeze pressure, a combination of internal and external anal sphincter function, was normal in all four groups. Hence no evidence was found of sphincteric damage suffered as a result of the surgery. There was also no difference in the length of the anal sphincter HPZ in the four groups. The sensory threshold of the anal canal mucosa as determined by electrosensitivity was similarly normal in all four groups.

In contrast, neorectal capacity was markedly and significantly lower after coloanal anastomosis than in the group of patients with ≥ 4 cm of residual rectum, and was also lower than in patients with an intact rectum. This finding confirms previous work by other investigators[4,11,12], who have suggested that improvement in this parameter correlates with improved clinical function. However, as a result of this study, we believe that it is not simply increased reservoir capacity that results in better continence, but that true coordinated activity exists between a capacious neorectum and the anal sphincter.

The rectoanal inhibitory reflex was first described by Gowers[13] in 1877. In 1964, Bennett and Duthie first investigated the reflex in detail[14] and postulated a role for it in anal sphincter sampling and fine control of anal continence. The key to this fine control of defaecation lies in graduated reflex inhibition of the anal sphincter, a decrease in pressure occurring in the upper part of the sphincter while a significant pressure differential is maintained in the lower part. In the light of the clinical results described, this is unlikely to be the same coordinated mechanism that we have observed in patients after very low anterior resection. The minor faecal leakage reported by 18 of the present patients implies that anal sphincter relaxation after very low anastomosis is excessive and does not genuinely represent coordination between the neorectum and anal sphincter. The extent of relaxation produced in the whole sphincter (*Figure 3*) together with the relatively small volume of neorectal distension required to produce such relaxation may explain why many patients were incontinent after coloanal or very low colorectal anastomosis.

In conclusion, it seems that the clinical functional outcome after anterior resection is related to the level of the anastomosis, as other authors have also shown[15]. The greater the length of residual rectum, the greater is the capacity of the neorectum. Distension of a neorectum of small capacity above the anal sphincter evokes such a degree of reflex inhibition of the whole anal sphincter that urgency and minor faecal leakage become almost inevitable. As this may last longer than 1 year, it is probably permanent.

The practical implications of these findings for the surgical treatment of rectal cancer depend on the site of the presenting rectal tumour. For carcinoma of the lower half of the rectum, where complete rectal excision is mandatory, the construction of a colonic J pouch anastomosed to the upper anal canal[16–18] should be considered. By increasing neorectal capacity, continence is said to be improved. For tumours of the upper half of the rectum, the results of the present study strongly suggest that, provided local recurrence can be avoided by obtaining adequate lateral circumferential margins[19,20] and provided that at least 2 cm of normal bowel wall can be excised distal to the growth[21], then the patient's quality of life will be better if >4 cm of distal rectum above the anal canal HPZ can be preserved.

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Prevention of cardiovascular effects of endotoxaemia by monoclonal antibodies specific for core endotoxin

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Passive immunization with antibody to the core region of endotoxin (core lipopolysaccharide (LPS)) has been reported to reduce mortality in severe sepsis. A rat model of endotoxaemia that reproduces the hyperdynamic cardiovascular state seen in early sepsis was developed to test monoclonal antibodies specific for core LPS. A thermodilution technique of measuring cardiac output was adapted for use in rats. Twenty-five animals were anaesthetized and mechanically ventilated with monitoring of central venous pressure and mean arterial pressure. Fluid replacement was adjusted to maintain the central venous pressure. Controls ($n = 10$) *and antibody-treated animals* ($n = 5$) *showed no significant change in cardiac output. Animals given 0·1 mg kg*$^{-1}$ *R2 endotoxin over 1 h* ($n = 5$) *showed a significant rise in cardiac output of 65 per cent* ($P < 0{\cdot}01$)*. This was abolished in rats given both antibody and endotoxin* ($n = 5$)*. This study provides evidence that a monoclonal antibody against core LPS abolishes the hyperdynamic state induced by endotoxin infusion.*

The sepsis syndrome with subsequent multiple organ failure continues to be a major cause of mortality among critically ill surgical patients[1]. Macrophage stimulation, releasing cytokines such as tumour necrosis factor and other secondary mediators, is the major cause of this syndrome[2]. Macrophage stimulation may be provoked by circulating endotoxin derived from a source of Gram-negative infection or, more commonly, from the patient's own gut flora[3–5]. Endotoxin, which is known chemically as lipopolysaccharide (LPS), is a major constituent of the outer cell wall of Gram-negative aerobic bacilli. The core region of the molecule (core LPS) is similar in structure and chemical composition in most pathogenic Gram-negative bacilli[6]. Passive immunization with polyclonal human antibody specific for core LPS, may be beneficial in critically ill patients[7–10]. Monoclonal antibodies specific for core LPS were developed and the efficacy of these tested in a small animal model simulating the cardiovascular derangements seen in human sepsis. A whole-chest thermodilution method of measuring cardiac output in the rat was developed. Its accuracy was verified by comparison with measurements determined by an electromagnetic flowmeter. An endotoxaemic rat model was developed with which to test the efficacy of these antibodies.

Materials and methods

Animals

Male Sprague–Dawley rats weighing between 250 and 450 g were used They were kept under standard conditions of heat and light, and provided food and water *ad libitum* until the time of experiment.

Monoclonal antibody

H513.23 is a murine monoclonal immunoglobulin G_{2a} specific for core LPS It was produced by a collaboration between the University Department of Surgery, the Preclinical Research Division of Sandoz, Switzerland, and the Scottish National Blood Transfusion Service, Edinburgh. *In vitro* testing of H513 23 demonstrated specific binding to a range of clinically relevant endotoxins (unpublished data).

Cardiac output measurements

Thermistors were salvaged from pulmonary artery flotation catheters and mounted in 2-Fr catheters (Portex, Hythe, UK)

After induction of anaesthesia, under aseptic conditions, a ventral incision was made in the neck, and the right common carotid artery and external jugular veins isolated and controlled.

A thermistor catheter was inserted into the common carotid artery, advanced into the aortic root and secured A 3-Fr polyethylene catheter (Portex) cut to a length of 20 cm was inserted through the external jugular vein into the right atrium Cardiac output measurement was made by injecting a bolus of 155 μl saline at room temperature into the right atrium. Temperature change registered by the thermistor was analysed by a personal computer program written in Turbo-Pascal 4 (Borland, Scotts Valley, USA) to produce a thermodilution curve. The area under the curve allowed calculation of the cardiac output

Measurement of arterial pressure and central venous pressure

Mean arterial pressure was measured through a 3-Fr polyethylene catheter in the right femoral artery. Central venous pressure was measured from the right atrial line.

Experiment 1

Nine rats were anaesthetized by intramuscular injection of 0·3 ml kg^{-1} Hypnorm (fentanyl 0·315 mg ml^{-1} and fluanisone 10 mg ml^{-1}; Veterinary Drug Company, York, UK). Vascular cannulas and a right femoral venous line were placed as described. Tracheostomy was performed and the animals mechanically ventilated with room air. Through a midline sternotomy the aortic arch was identified, cleaned and a 2-mm electromagnetic flow probe (Blood Flow Meter, Model SP2202; Gould Statham, Hato Rey, Puerto Rico) placed around it between the innominate and left common carotid arteries. A ligature was placed around the origin of the innominate artery ensuring that all the cardiac output, less the coronary circulation, passed through the aortic arch. The chest wall was closed around the lead of the flow probe. A variety of high and low output cardiovascular states were then induced by controlled haemorrhage via the arterial line, reperfusion of shed blood through the femoral vein line and infusion of dopamine hydrochloride (Abbott, Queensborough, UK) at a rate of 10–20 μg kg^{-1} min^{-1}. Simultaneous determinations of cardiac output measured by the electromagnetic flowmeter and whole-chest thermodilution method were taken. The animals were killed at the end of each procedure.

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Experiment 2

Twenty-five rats were anaesthetized and underwent tracheostomy and mechanical ventilation with a mixture of 1 per cent halothane, 69 per cent nitrous oxide and 30 per cent oxygen. Thermistor and vascular lines were placed as before. All the animals were infused with gelatin solution (Haemaccel; Hoechst, Hounslow, UK) and fluid replacement adjusted to keep central venous pressure between 3·5 and 4·5 mmHg throughout the experiment. Body temperature was maintained between 37 and 38°C using a radiant heat source. All animals were allowed to recover for a period of 1 h, at which time measurements of mean arterial and central venous pressures were taken Cardiac output was measured by whole-chest thermodilution, at least two measurements were taken at each time point This first observation point was designated as $T = 0$ min. Readings were repeated every 60 min up to 240 min. The animals were then killed.

Experimental groups

Animals were divided into four groups. Group 1 ($n = 10$) were controls and received fluid resuscitation only. Group 2 ($n = 5$) contained LPS-treated animals which received an infusion of 0·1 mg kg^{-1} R2 LPS (extracted from an R2 core type rough mutant of *Escherichia coli*) from $T = 0$ to $T = 60$ min. Group 3 ($n = 5$) consisted of antibody-treated rats. These received 10 mg kg^{-1} H513.23 at $T = -15$ min. The volume of antibody solution was approximately 0·3 ml, which was infused slowly over a period of 5 min. Group 4 ($n = 5$) contained antibody- and endotoxin-treated animals. These were pretreated at $T = -15$ min with 10 mg kg^{-1} H513.23 followed by an infusion of 0·1 mg kg^{-1} R2 endotoxin from $T = 0$ to $T = 60$ min.

Statistical methods

Correlation between the electromagnetic flow rates and thermodilution cardiac output measurements were analysed by calculation of the coefficient of correlation and numerical agreement with the method of Bland and Altman[11]. For comparison of cardiac output between the experimental groups in experiment 2, two summary statistics were chosen[12] and compared using Student's unpaired *t* test The summary statistics used were maximum change in cardiac output and the mean area under the curve of cardiac output *versus* time for each group This latter figure was an estimate of total cardiac output in each group over the observation period

Results

Experiment 1

A total of 258 paired estimations of cardiac output were obtained and plotted on a scattergram (*Figure 1*). There was

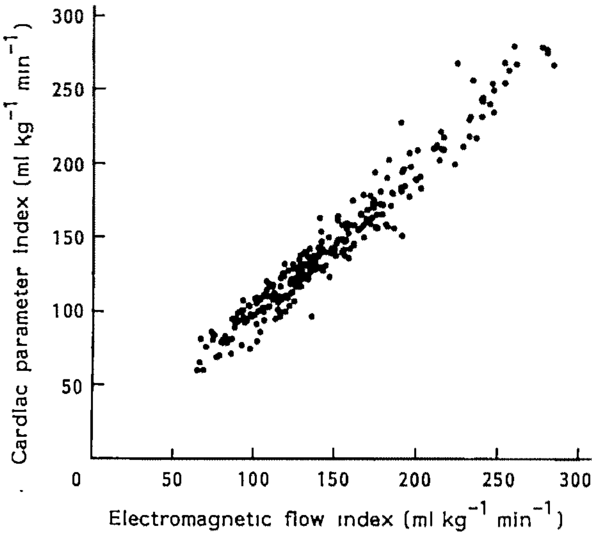

Figure 1 *Scattergram showing cardiac parameter (thermodilution cardiac output) plotted against electromagnetic flow rate in the rat aortic arch Values are indexed according to body-weight.* $r = 0{\cdot}98$, $P < 0{\cdot}001$

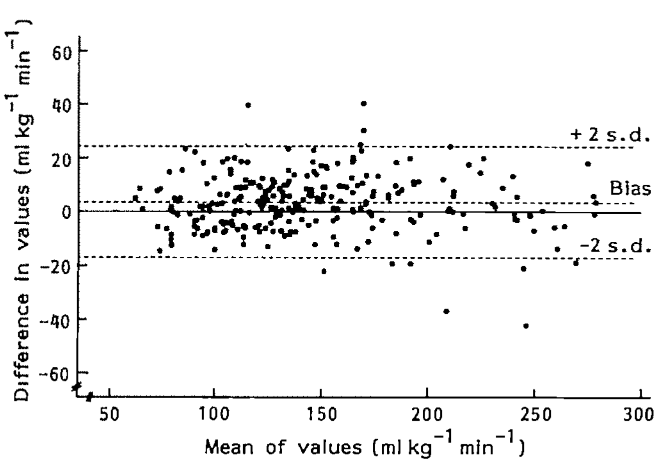

Figure 2 *Bland–Altman plot showing the difference between each pair of thermodilution cardiac output and electromagnetic flow rate readings plotted against their mean value. The mean of the differences (bias) is 3·27 ml kg^{-1} min^{-1} (normal range (2 s.d.) 20·97 ml kg^{-1} min^{-1})*

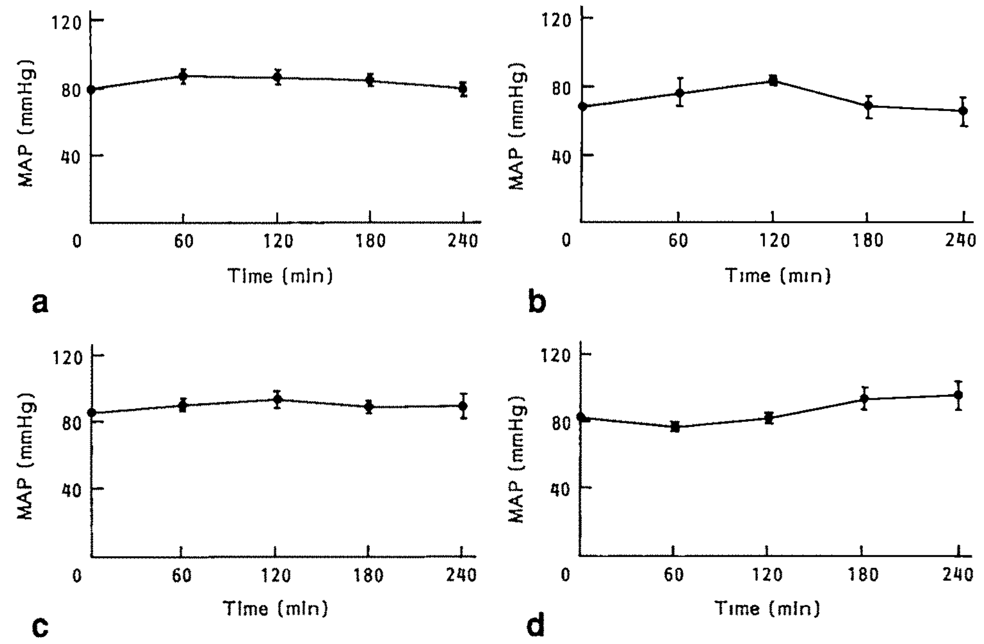

Figure 3 *Mean(s.e m.) arterial pressure (MAP) plotted against time* **a** *Group 1 control animals* (n = *10*). **b** *Group 2 lipopolysaccharide-treated animals* (n = *5*). **c** *Group 3 antibody-treated animals* (n = *5*). **d** *Group 4 antibody- and endotoxin-treated animals* (n = *5*)

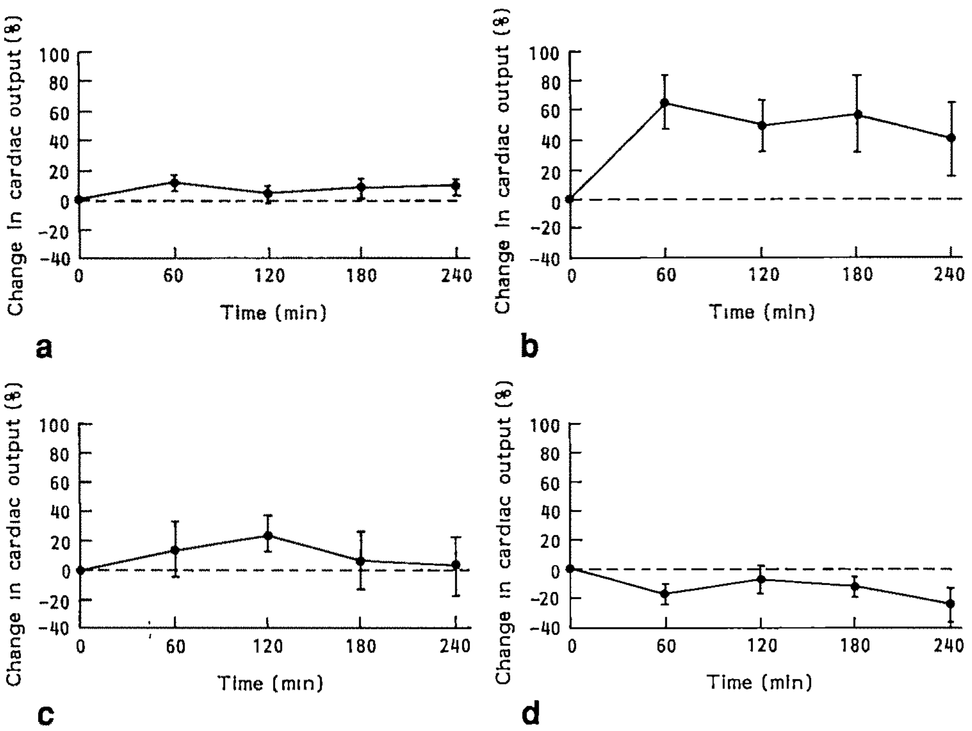

Figure 4 *Mean(s.e.m.) percentage change in cardiac output plotted against time.* **a** *Group 1 control animals* (n = *10*) **b** *Group 2 lipopolysaccharide-treated animals* (n = *5*) **c** *Group 3 antibody-treated animals* (n = *5*). **d** *Group 4 antibody- and endotoxin-treated animals* (n = *5*)

a high degree of correlation between the two methods. The degree of arithmetical agreement between the methods was analysed in a Bland–Altman plot (*Figure 2*). The difference in measurement between each method was plotted against the mean of the two measurements, the mean(2 s.d.) of the differences was 3·27(20·97) ml kg^{-1} min^{-1}.

Experiment 2

The results of measurements of mean arterial pressure and cardiac output in the four experimental groups are shown in *Figures 3* and *4*. Central venous and mean arterial pressures were similar throughout the procedure for all groups. The cardiac output in the control animals (group 1) remained close to the baseline level throughout the observation period. The animals pretreated with H513.23 (group 3) showed a rise in cardiac output which reached a maximum at $T = 120$ min, but this was not significantly different from that in the control group. The animals treated with R2 LPS (group 2) showed a rise in cardiac output that was maximal at 1 h. Using both peak cardiac output and mean area under the curves, the increase in cardiac output in the LPS-treated animals was significant compared with controls (maximal increase in cardiac output: $t = 3{\cdot}7$, $P < 0{\cdot}01$; area under the cardiac output curves: $t = 2{\cdot}7$, $P < 0{\cdot}05$; 13 d.f.). In the group pretreated with H513.23 and then administered LPS (group 4) this increase in cardiac output was abolished despite maintenance of normal central venous and mean arterial pressures.

Discussion

The sepsis syndrome and multiple organ failure continue to be a major clinical problem in critically ill patients. Treatment of such patients with antibody specific for core LPS may confer benefit in terms of reduced mortality. Initial trials have used human polyclonal antibody derived from two different sources. Braude's group[7] collected serum from volunteers who had been inoculated with heat-killed J5 *E. coli* rough mutant (with only core LPS on their cell surface). Gaffin *et al.*[8] screened a normal blood donor population for individuals who had a high endogenous anticore LPS antibody activity. Such blood was processed to produce an immunoglobulin fraction rich in anticore LPS antibody. Inoculation of volunteers with heat-killed organisms is no longer acceptable and the amount of antibody available from blood donors with high endogenous anticore LPS antibody is limited. The danger of transmission of infection is a further problem with these methods. Groups have sought to develop monoclonal antibodies specific for core LPS[13,14].

The cardiovascular derangements in early human sepsis include systemic vasodilatation, increased cardiac output and decreased systemic vascular resistance.

An accurate, reliable and reproducible method of cardiac output measurement had to be devised. The thermodilution method has been shown to be accurate and reliable in large animals and humans[15], although doubts about its accuracy in small animals have been raised. Isoyama *et al.*[16] showed that thermistors available for clinical use are suitable for measuring temperature change in the small vessels and relatively low flow states seen in the rat. In small animals it is necessary to measure the whole-chest thermodilution curve with the injection site in the right atrium and the sampling site in the ascending aorta Hayes *et al.*[17] showed that the mechanics of heat distribution through the chest alters the shape of the thermodilution curve and makes interpretation difficult. In pilot experiments mathematical constants that correct for these factors in the computation of cardiac output were derived. By applying these constants to the cardiac output calculations these experiments demonstrate that cardiac output measurements correlate with estimates obtained by electromagnetic flowmeter measurement over a wide range of values.

The whole-chest thermodilution method shows that suitably anaesthetized rats can be maintained in a steady cardiovascular state over a period of 4 h. Administration of a relatively small dose of endotoxin infused over a period of 1 h and supported by fluid resuscitation results in a significant increase in cardiac output. This increase can be abolished by pretreatment with H513.23 monoclonal antibody specific for core LPS.

The cardiovascular changes seen in this model, i.e. high cardiac output associated with normal central venous and mean arterial pressures, are similar to those seen in patients suffering from the sepsis syndrome. Since the cardiovascular changes in this model are initiated by infusion of highly purified endotoxin derived from a known species of Gram-negative aerobic bacillus, it will be possible to compare different combinations of antibody and endotoxin to assess the cross-reactivity of the different monoclonal antibodies. It is hoped that antibodies will be identified that have *in vivo* cross-reactivity against endotoxins derived from the Gram-negative bacilli that most commonly colonize the human gut and/or are involved in infection. Such antibodies may have a useful role in the treatment of the sepsis syndrome.

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Prognostic significance of regional lymph node reaction after curative resection of advanced gastric cancer

The prognosis of patients with advanced gastric cancer who undergo curative resection is still unsatisfactory. The relationship between prognosis and various factors such as stage, lymph node metastasis, serosal invasion and regional lymph node reaction (follicular hyperplasia and sinus histiocytosis) was evaluated. Of the factors studied, the only one that correlated well with survival was sinus histiocytosis. Lymph node metastasis was related weakly to prognosis. No correlation between prognosis and stage, serosal invasion or follicular hyperplasia was observed. Sinus histiocytosis may represent the morphological tumour–host immune reaction. Lymph node metastases or histological types were not related to regional lymph node reaction. These results suggest that sinus histiocytosis could be a useful prognostic factor for gastric cancer. Intensive postoperative follow-up for recurrence may be necessary even for patients with low-grade sinus histiocytosis in whom curative surgery is attempted.

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The survival rate of patients with gastric cancer has improved owing to the early detection of cancer and to progress in surgery, chemotherapy and immunotherapy. The 5-year survival rate for early gastric cancer[1–3] is >90 per cent. However, in patients with advanced gastric cancer who undergo curative resection the 5-year survival rate[4–6] varies from 28 to 61 per cent.

There are a number of prognostic factors for gastric cancer. Maruyama *et al.*[5] reported that factors such as peritoneal, liver and distant lymph node metastases, and Borrmann type IV cancer (diffusely infiltrating carcinoma) could reduce the success of surgical treatment. Kodama *et al.*[1] reported that lymph node metastases and serosal invasion significantly affect the 5-year survival rate.

It is known that the tumour-bearing host mounts an immune response against its own neoplasm, chiefly by cell-mediated immunity[7]. Experimentally, regional lymph nodes are capable of interfering with the growth of tumour cells[8]. Regional lymph nodes may block the implantation and growth of distant metastases[9]. These results suggest that regional lymph nodes may play an important role in the development of cancer. Initially Black *et al.*[10] reported that sinus histiocytosis in regional lymph nodes in breast cancer correlated well with the survival rate. They also observed that follicular hyperplasia in the regional lymph nodes was associated with longer survival[11]. In a previous study it has been shown that postoperative survival of patients with oesophageal cancer correlated with sinus histiocytosis responses in regional lymph nodes[12].

The aim of this study was to evaluate the relationship between prognosis and factors such as cancer stage, lymph node metastases, serosal invasion and regional lymph node reaction in patients with gastric cancer undergoing curative surgery.

Patients and methods

From 1975 to 1986, 102 patients with stage II and III gastric cancer underwent curative gastrectomy in this department (*Table 1*). All had primary adenocarcinoma of the stomach and no synchronous or metachronous carcinoma. No patient received any anticancer therapy before surgery. After surgery 41 patients received chemotherapy with the 5-fluorouracil analogue tegafur (ftorafur FT; Taiho, Tokyo, Japan), 46 received immunochemotherapy with OK-432 and tegafur, and 15 had no additional therapy. The patients' ages ranged from 32 to 81 years. Operative findings, microscopic findings and curability were assessed and described according to the criteria of the Japanese Research Society for Gastric Cancer[13]. Briefly, stage II includes microscopic nodal metastasis surrounding the stomach (n1(+)) and/or microscopic wall invasion in the subserosal layer with no macroscopic liver metastasis and no peritoneal dissemination; stage III includes microscopic nodal metastasis along the main arteries including the coeliac axis (n2(+)) and/or microscopic wall invasion in the serosal layer with no macroscopic liver metastases or peritoneal dissemination. Tumours with invasion of the gastric wall no deeper than the subserosal layer were included in the category of cancers with negative serosal invasion. Any cancer with invasion of a serosal surface exposed to the peritoneal cavity was classified as a cancer with positive serosal invasion. The criteria for curative resection included: (1) no macroscopic liver metastases or peritoneal dissemination and no other distant metastases; (2) no residual cancer cells at the resection margins; and (3) no lymph node metastasis or resectable positive nodes. Histological type was taken as that with the most extensive histological pattern in the specimen.

Fifty-one patients are still alive and 51 have died from tumour recurrence.

The evaluation of microscopic lymph node reaction was performed in all 102 patients. A total of 3267 lymph nodes were examined. Sinus

Table 1 *Characteristics of 102 patients with advanced gastric cancer*

	No. of patients
Sex ratio (M:F)	63:39
Postoperative therapy	
None	15
Chemotherapy	41
Immunochemotherapy	46
Stage	
II	48
III	54
Serosal invasion	
Negative	47
Positive	55
Lymph node metastasis	
Negative	17
Positive	
n1	52
n2	33

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Table 2 *Grade of regional lymph node reaction*

Grade	Description
Follicular hyperplasia	
0	Germinal centres rare
1	Germinal centres recognizable in cortex
2	Germinal centres recognizable in cortex and medulla
3	Germinal centres recognizable in all lymph node areas
Sinus histiocytosis	
0	Sinus not seen in lymph node area
1	Sinus $<\frac{1}{4}$ in lymph node area
2	Sinus $\frac{1}{4}$–$\frac{1}{2}$ in lymph node area
3	Sinus $>\frac{1}{2}$ in lymph node area

histiocytosis consisted of a dilated sinus with well defined edges filled with pale uniform histiocytes. Follicular hyperplasia was defined as the presence of lymphoid follicles with clear and reactive centres (germinal centre). The grade of sinus histiocytosis and follicular hyperplasia was assessed from the sections of all dissected lymph nodes routinely stained with haematoxylin and eosin according to a previous report[11] (*Table 2*). Grades 0 and 1 were regarded as negative, and grades 2 and 3 as positive. The highest grade in each patient was used. All sections were read by two of the authors, who were not aware of the clinical characteristics of the patients.

Statistics

The Kaplan–Meier method was used for calculation of the postoperative survival rate, and the generalized Wilcoxon test employed to determine the statistical significance of differences. Multivariate analysis was performed by the proportional hazards model, with the postoperative survival time in days used as the outcome to compare variables. The χ^2 test with Yates' correction was also used. $P<0·05$ was considered statistically significant.

Results

The cumulative survival rate at 5 years in patients with stage II gastric cancer was 56 per cent, while that of those with stage III cancer was 44 per cent (*Figure 1*). The survival rate of stage II patients was slightly higher than that of stage III patients, but not significantly so. Therefore, the following analyses were performed by grouping patients with stage II and III cancer.

The cumulative survival rate was compared between 17 patients with negative nodes and 85 with positive nodes (n1(+) and n2(+)) (*Figure 2a*). The survival rate at 5 years in node-negative patients was 65 per cent, while that of node-positive patients was 47 per cent. The difference between these two survival rates approached statistical significance ($P<0·1$).

The survival rate at 5 years in patients with negative serosal invasion was 59 per cent, while that of those with positive serosal invasion was 42 per cent. There was no significant difference between the two groups (*Figure 2b*).

The cumulative survival rate at 5 years in 76 patients without follicular hyperplasia was 50 per cent, while that of 26 with hyperplasia was 49 per cent (*Figure 3a*). There was no significant difference between the two groups.

The cumulative 5-year survival rate in 37 patients without sinus histiocytosis was 29 per cent, while that of 65 with histiocytosis was 65 per cent (*Figure 3b*). The survival rate of patients with sinus histiocytosis was significantly greater than that of those without ($P<0·01$). Sixteen patients without sinus histiocytosis were treated with tegafur, 14 were treated with tegafur and OK-432, and seven had no therapy, while of patients with sinus histiocytosis, 27 were treated with tegafur, 31 with tegafur and OK-432, and seven had no therapy. There was no significant difference in treatment after therapy between these two groups ($\chi^2 = 1·68$, 2 d.f., $P = 0·43$).

The relationship between survival rate and lymph node reaction was examined in 85 patients with nodal metastases. The cumulative survival rate at 5 years in 60 patients without follicular hyperplasia but with lymph node metastases was 46 per cent, while that of 25 with follicular hyperplasia and lymph node metastases was 51 per cent (*Figure 4a*). There was no significant difference between the two groups.

The cumulative survival rate at 5 years in 33 patients with lymph node metastases and no sinus histiocytosis was 28 per cent, while that of 52 with lymph node metastases and sinus histiocytosis was 62 per cent (*Figure 4b*) ($P<0·05$).

Multivariate analysis was performed to determine the most useful prognostic factor. Only sinus histiocytosis was significantly related to survival (*Table 3*).

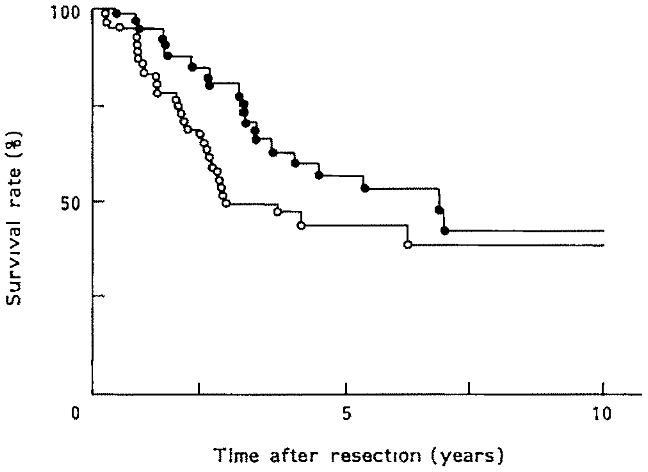

Figure 1 *Cumulative survival rate in patients with stage II and III gastric cancer who underwent curative resection.* ●, *Stage II* (n = *48*), o, *stage III* (n = *54*)

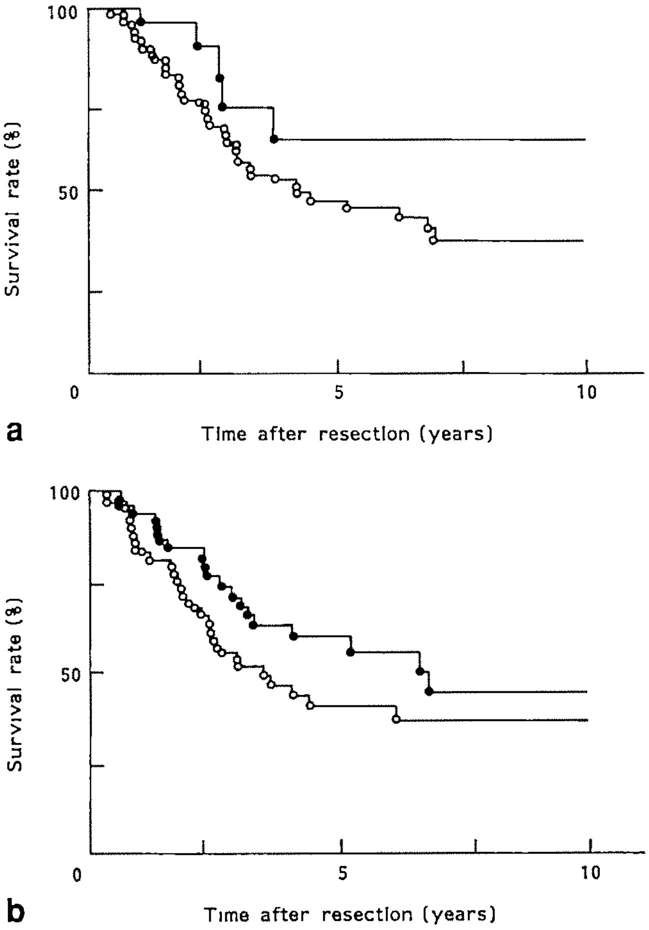

Figure 2 **a** *Cumulative survival rate in patients without* (●, n = *17*) *and with* (o, n = *85*) *nodal metastasis.* **b** *Cumulative survival rate in patients without* (●, n = *47*) *and with* (o, n = *55*) *serosal invasion*

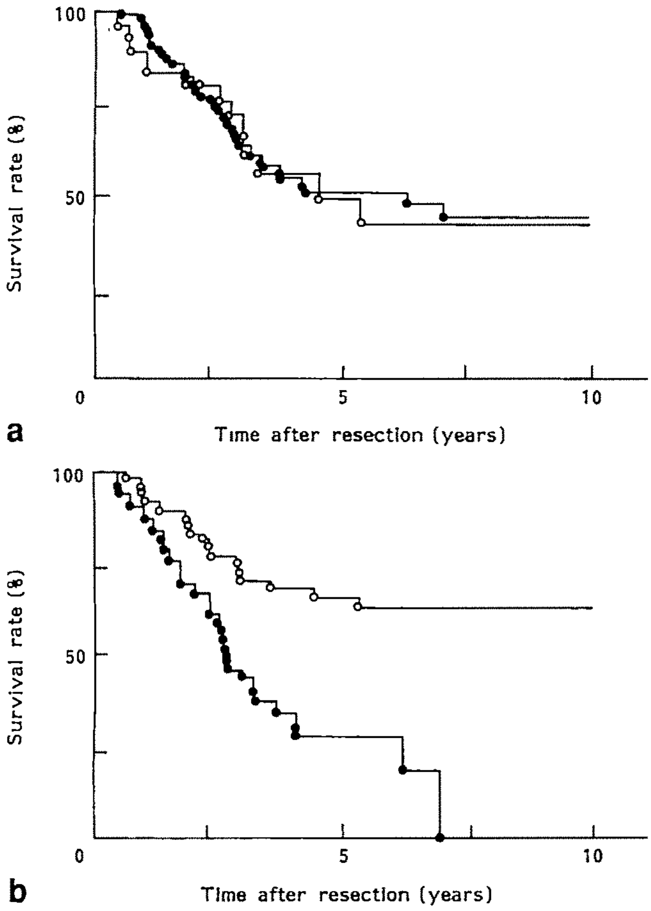

Figure 3 *Relationship between survival rate and regional lymph node reaction* **a** *Follicular hyperplasia.* ●, *negative cases* (n = *76*); ○, *positive cases* (n = *26*). **b** *Sinus histiocytosis.* ●, *negative cases* (n = *37*), ○, *positive cases* (n = *65*)

Table 3 *Multivariate analysis of various prognostic factors related to length of survival in 102 patients with gastric cancer*

Variable*	χ^2	P
Stage (II *versus* III)	0·013	0·836
Serosal invasion	1·551	0·124
Lymph node metastasis	0·185	0·538
Follicular hyperplasia	0·105	0·747
Sinus histiocytosis	7·019	0·009

*The proportional hazards model was used to test the significance of the presence or absence of each variable (except stage) 1 d.f

Table 4 *Correlations between lymph node reaction and lymph node metastases in 102 patients with gastric cancer*

	Lymph node reaction			
	Follicular hyperplasia		Sinus histiocytosis	
Lymph node metastases	Negative	Positive	Negative	Positive
Negative (n = 17)	16	1	4	13
Positive (n = 85)	60	25	33	52

Lymph node reaction was compared between 17 patients with negative nodes and 85 with positive nodes. There were no correlations between lymph node reaction and lymph node metastases (follicular hyperplasia $\chi^2 = 2·98$; sinus histiocytosis: $\chi^2 = 0·85$; 4 d.f.) (*Table 4*).

Histologically, the tumours showed tubular adenocarcinoma in 41 patients, poorly differentiated adenocarcinoma in 36, signet-ring cell carcinoma in 17, mucinous adenocarcinoma in five and papillary adenocarcinoma in three. There was no relationship between lymph node reaction and histological type (follicular hyperplasia: $\chi^2 = 6·14$; sinus histiocytosis: $\chi^2 = 0·50$; 4 d.f.) (*Table 5*).

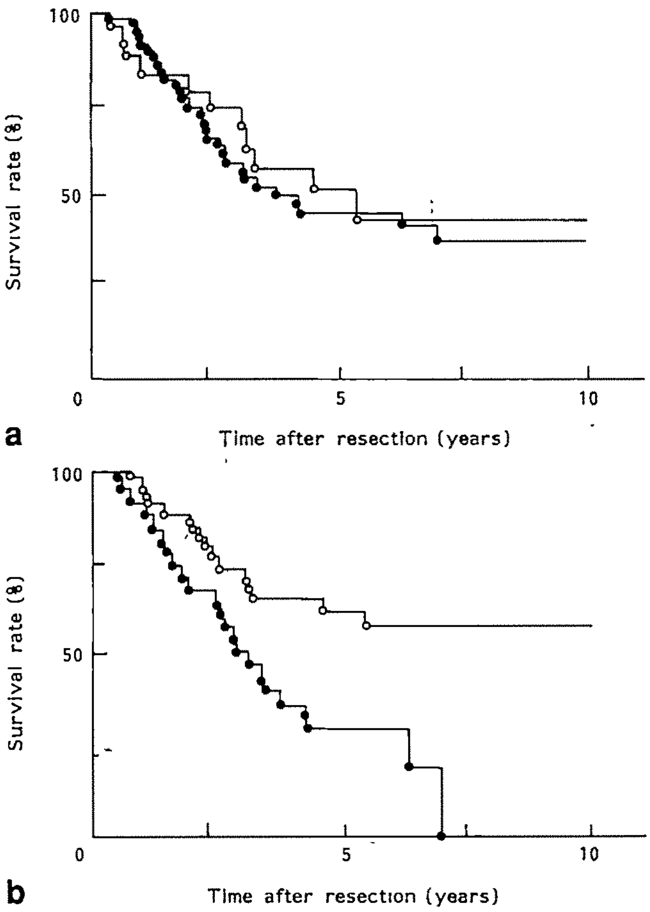

Figure 4 *Relationship between survival rate and regional lymph node reaction in patients with nodal metastasis.* **a** *Patients without* (●, n = *60*) *and with* (○, n = *25*) *follicular hyperplasia* **b** *Patients without* (●, n = *33*) *and with* (○, n = *52*) *sinus histiocytosis*

Discussion

The analysis of postoperative prognostic factors for gastric cancer may be useful for the selection of postoperative therapy and follow-up study. If a patient is at high risk for tumour recurrence, aggressive chemotherapy and intensive follow-up may be required after operation.

Lymph node metastases and depth of invasion can be considered the major prognostic factors after attempted curative resection of advanced gastric cancer. Baba *et al.*[14] carried out univariate and multivariate analyses in patients who underwent curative resection for advanced carcinoma of the stomach and identified tumour stage, lymph node metastases and depth of invasion as important prognostic factors. Boku *et al.*[6] also reported that the higher the aggregate total of serosal invasion and lymph node metastasis factors, the lower the 5-year survival rate. To analyse the prognostic factors for gastric cancer in this study, patients with stage II and III cancer were selected because half of these patients die from tumour recurrence. There was no significant difference in the survival rate between the two groups. Thus subsequent analyses were carried out on all patients combined. The prognosis of patients without nodal metastases may be slightly better than those with such metastases; however, a significant difference was not found. Moreover, the prognosis of patients with serosal invasion was similar to that in those without. Therefore neither lymph node metastases nor serosal invasion could be identified

Table 5 *Relationship between lymph node reaction and histological type in 102 patients with gastric cancer*

Histological type of adenocarcinoma	No. of patients	Lymph node reaction			
		Follicular hyperplasia		Sinus histiocytosis	
		Negative	Positive	Negative	Positive
Papillary	3	3	0	1	2
Tubular	41	27	14	15	26
Poorly differentiated	36	26	10	13	23
Mucinous	5	5	0	2	3
Signet-ring cell	17	15	2	6	11
Total	102	76	26	37	65

as significant prognostic factors in patients with stage II and III cancer. This failure to confirm well known prognostic factors may be due to small sample size.

Black *et al.*[10] presented an initial report that high-grade sinus histiocytosis in the axillary nodes of patients with breast cancer is almost invariably associated with a survival of 5 years or more regardless of the presence of axillary metastases Many reports have suggested that sinus histiocytosis is correlated with a better prognosis in various cancers, such as those of the breast, colon and oesophagus[12,15–18]. The evaluation of follicular hyperplasia is different. Many authors have indicated that there is no correlation between follicular hyperplasia and prognosis[12,16–18], but some reports do support such a relationship[11,19]. Black *et al.*[11] reported that in gastric cancer follicular hyperplasia was associated with longer survival and that sinus histiocytosis was seen infrequently The present study indicates that the prognosis of patients with sinus histiocytosis is better than that of those without, while follicular hyperplasia has no effect on prognosis.

Multivariate analysis demonstrated that sinus histiocytosis is the only independent variable associated with survival. In patients with nodal metastases, sinus histiocytosis was associated with longer survival. This lymph node reaction is considered to represent a tumour–host reaction[16]. Experimental results have suggested that regional lymph nodes are capable of interfering with the growth of tumour cells[8]. Analysis of T cell subsets in the lymph node using monoclonal antibodies indicates that T cells predominate in the paracortical area, whereas B cells comprise the predominant cell type in follicular areas[20]. Thus, sinus histiocytosis in the paracortical area may represent the activation of both T cells and macrophages. Patt *et al.*[16] assumed that sinus histiocytosis represented morphological evidence of cell-mediated immunity, while follicular hyperplasia may be an aspect of the antibody-mediated immune response. Since T cells and macrophages (histiocytes) play a major role in cancer immunity, sinus histiocytosis in regional lymph nodes may be a local antitumour reaction.

Lymph node metastases or histological type may influence lymph node reaction. The relationship between lymph node reaction and lymph node metastases or histological type was examined in the present study and no correlation was found Thus, these factors do not appear to be related to regional lymph node reaction.

Finally, in the present study sinus histiocytosis was found to be a more sensitive prognostic factor than either lymph node metastases or serosal invasion in patients with advanced gastric cancer. Patients with low-grade sinus histiocytosis may require more intensive follow-up for recurrence after surgery.

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Survival after hepatic resection for malignant tumours

A retrospective analysis of 194 patients who underwent hepatic resection for primary or metastatic malignant disease from January 1962 to December 1988 was undertaken to determine variables that might aid the selection of patients for hepatic resection. Hepatic metastases were the indication for resection in 126 patients. The 5-year survival rate was 17 per cent. For patients with resected metastases from colorectal cancer ($n = 104$)*, the survival rate at 5 years was 18 per cent. The 5-year survival rate was 27 per cent when the resection margin was* >5 *mm compared with 9 per cent when the margin was* $\leqslant 5$ *mm* ($P < 0{\cdot}01$)*. No patient with extrahepatic invasion, lymphatic spread, involvement of the resection margin or gross residual disease survived to 5 years, compared with a 23 per cent 5-year survival rate for patients undergoing curative resection* ($P < 0{\cdot}02$)*. The survival rate of patients with poorly differentiated primary tumours was nil at 3 years compared with a 20 per cent 5-year survival rate for patients with well or moderately differentiated tumours* (P *not significant*)*. The site and Dukes' classification of the primary tumour, the sex and preoperative carcinoembryonic antigen level of the patient, and the number and size of hepatic metastases did not affect the prognosis. The 5-year survival rate for patients with hepatocellular carcinoma* ($n = 42$) *was 25 per cent. An improved survival rate was found for patients whose α-fetoprotein level was normal (37 per cent at 5 years) compared with those having a raised level (nil at 3 years)* ($P < 0{\cdot}01$)*. Involvement of the resection margin, extrahepatic spread and spread to regional lymph nodes were associated with an 8 per cent 5-year survival rate* versus *44 per cent for curative resection* ($P < 0{\cdot}005$)*. The presence of cirrhosis, the presence of symptoms, and the multiplicity and size of the tumour did not affect the prognosis. The 5-year survival rate of 11 patients with hepatic sarcoma was 25 per cent. No patient with peripheral cholangiocarcinoma survived to 1 year in contrast to patients with hilar cholangiocarcinoma, all four of whom survived for more than 14 months.*

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A previous study[1] has shown a reduction in overall operative mortality rates following hepatic resection from 19 per cent between 1962 and 1979 to 9·7 per cent after 1980. Further, the operative mortality rate after resection of benign hepatic neoplasms was nil compared with 4·8 per cent for resection of hepatic metastases and 20·4 per cent for resection of primary hepatic neoplasms performed after 1980[1]. This study has been extended to analyse the determinants of long-term survival in patients who have undergone hepatic resection for malignant disease.

Patients and methods

Patients ($n = 478$) who underwent liver resection from January 1962 to December 1988 were identified by computer search of all records in the medical records and pathology departments. Of 194 patients included in the study, 68 had undergone major resection of primary malignant hepatic tumours and 126 resection of metastases. The results of segmental or wedge excision of tumours were included if surgery was curative.

Couinaud's classification of hepatic resection was employed regardless of the nomenclature used in the operative report[1–3]. The reasons for exclusion of 284 charts were minor liver resection *en bloc* with other abdominal malignancy ($n = 40$), resection or biopsy of benign hepatic neoplasms ($n = 96$), post-traumatic liver resection ($n = 33$), wedge excision of one of many hepatic metastases ($n = 41$), hepatic transplantation ($n = 49$), miscellaneous resection or drainage of an abscess, excision of cyst or other non-malignant condition ($n = 21$) and donor hepatectomy ($n = 4$).

Surgery was classified as non-curative if the operation record described gross residual disease, direct spread to adjacent structures, or if there was involvement of the resection margin on histopathological examination or spread to the lymph nodes of the portal triad. Lymph node involvement regional to the primary tumour for those patients undergoing synchronous resection of a primary tumour and hepatic metastases did not preclude a curative hepatic resection. All other resections were classified as curative.

Demographic, clinical and operative data were collected by review of the hospital records and surgeons' office records. Follow-up data were obtained by postal and telephone enquiry from the referring hospital or surgeon, from the tumour registry, or from the town clerk's office. Five of the 478 records (1·04 per cent) were unobtainable. Complete follow-up data were obtained for all but five patients who had undergone hepatic resection (97·4 per cent): three were lost to follow-up between 2 and 4 years after surgery, and no trace was found of two patients.

Statistical analysis

The endpoint for survival analysis was death of the patient. Analyses were performed by the life-table method[4], differences between survival curves were assessed using the log rank test[5]. The odds ratios and their 95 per cent confidence interval (c.i.) for pairs of survival analyses were also calculated[6]. Patients who died after operation were included in the life-table analyses. Statistical significance was accepted for a two-tailed P value $<0{\cdot}05$.

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Table 1 *Ages of patients who underwent resection of malignant hepatic neoplasms*

Indication	No. of patients	Mean (range) age (years)
Primary hepatic malignancy	68	52·4 (2–82)
Hepatocellular carcinoma	42	54·2 (6–82)
Cholangiocarcinoma or gallbladder carcinoma	12	59·0 (30–77)
Hepatoblastoma	3	8·0 (2–13)
Sarcoma	11	50·4 (12–71)
Metastases	126	59·1 (6–80)
Colorectal cancer	104	60·1 (28–79)
Other primary sites	22	53·9 (6–80)

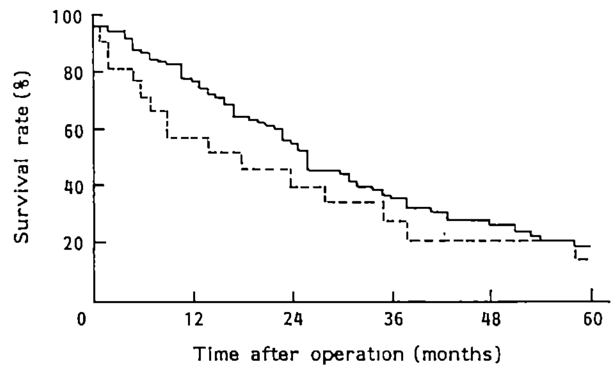
Table 2 *Extent of hepatic resection*

	Metastases		Primary		
	Colorectal	Other	HCC	Other	Total
Right hepatectomy	31	9	6	9	55
Left hepatectomy	8	5	10	3	26
Extended right hepatectomy	26	4	15	6	51
Extended left hepatectomy	5	0	3	0	8
Segmentectomy	18	2	5	8	33
Wedge resection	16	2	3	0	21
Total	104	22	42	26	194

HCC, hepatocellular carcinoma

Table 3 *Outcome of 22 patients who underwent hepatic resection of metastases from primary sites other than the colorectum*

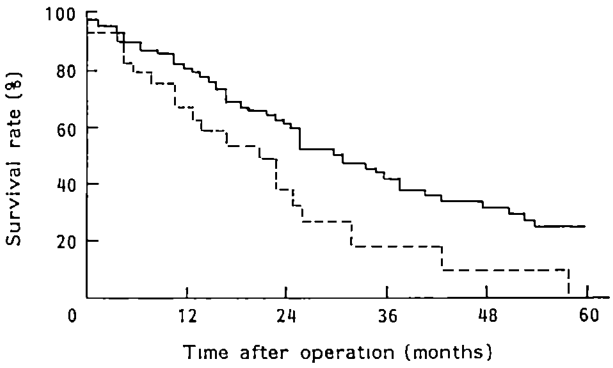
Patient no.	Primary	Operation	Curative	Survival (months)	Status
1	Gallbladder	Right hepatectomy	Yes	0·0	Operative death
2	Kidney	Segmentectomy	No	0·4	Lost to follow-up
3	Uterus	Right hepatectomy	Yes	1·1	Operative death
4	Pancreas	Right hepatectomy	No	2·6	Died from disease
5	Lung	Left hepatectomy	Yes	2·7	Died from disease
6	Stomach	Segmentectomy	No	5·8	Died from disease
7	Uterus	Right hepatectomy	No	6·2	Died from disease
8	Ileal carcinoid	Left hepatectomy	No	7·7	Died from disease
9	Ovary	Left hepatectomy	Yes	8·8	Alive and well
10	Kidney	Right hepatectomy	No	9·3	Died from disease
11	Kidney, Wilms' tumour	Segmentectomy	No	9·5	Died from disease
12	Unknown (pancreas)	Right hepatectomy	No	14·9	Died from disease
13	Ileal carcinoid	Right hepatectomy	No	15·9	Alive with recurrence
14	Unknown (pancreas)	Segmentectomy	No	18·1	Died from disease
15	Gallbladder	Right hepatectomy	Yes	24·4	Died from disease
16	Kidney	Right hepatectomy	Yes	28·0	Died from disease
17	Breast	Right hepatectomy	Yes	33·5	Alive and well
18	Ocular melanoma	Left hepatectomy	Yes	35·7	Died from disease
19	Unknown (colon)	Right hepatectomy	No	38·7	Died from disease
20	Thyroid	Left hepatectomy	Yes	58·1	Died from disease
21	Ileal carcinoid	Right hepatectomy	No	87·8	Alive with recurrence
22	Broad ligament embryonal cell tumour	Right hepatectomy	No	130·0	Alive and well



No. at risk

	0	12	24	36	48	60
Colorectal primary	104	74	44	26	15	10
Other site	22	13	8	5	4	3

Figure 1 *Survival curves for patients who underwent hepatic resection for metastases from colorectal cancer (——) and for metastases from primary carcinoma at other sites (– – –). P not significant (log rank test)*



No. at risk

	0	12	24	36	48	60
Curative	76	58	37	24	14	9
Non-curative	28	18	9	3	2	

Figure 2 *Survival curves for patients who underwent curative (——) and non-curative (– – –) hepatic resection of metastases from colorectal cancer* P < 0·02 *(log rank test)*

Results

Resection of metastases was the indication for hepatectomy in 126 patients; the site of the primary was the colon or rectum in 104. Of 68 patients who underwent resection of malignant tumours originating in the liver, histopathological examination showed hepatocellular carcinoma (HCC) in 42. Of these, three patients showed mixed HCC and cholangiocarcinoma, and cirrhosis was present in nine.

Histopathological examination of the remaining 26 primary hepatic malignant tumours revealed cholangiocarcinoma (12) including carcinoma of the gallbladder (four), hepatic sarcoma (11) and hepatoblastoma (three). Patients' ages are shown in *Table 1* and the extent of hepatic resection in *Table 2*

Metastases

The overall 5-year survival rate of patients who underwent resection of the liver for metastatic disease was 17 per cent. The 5-year survival rate was 18 per cent for patients with metastases from colorectal cancer *versus* 14 per cent for those with metastases from other primary sites (*Figure 1*). The site of the primary tumour and the outcome of patients with metastases from primary sites other than the colorectum is shown in *Table 3*. For three patients, the site of the primary was unknown at the time of hepatic resection. Subsequent investigation showed that these were metastases from the pancreas (two patients) and colon (one).

Metastases from colorectal cancer

The 5-year survival rate for 76 patients who underwent curative operation was 23 per cent Resection of metastases was non-curative in 28 patients: eight cases showed involvement of the resection margin, eight had gross residual disease, five showed direct spread to adjacent structures, and seven spread to lymph nodes of the portal triad. The 5-year survival rate for patients undergoing non-curative resection was zero ($P < 0{\cdot}02$) (*Figure 2*). The resection margin was the most significant prognostic indicator. A margin >5 mm was associated with a 5-year survival rate of 27 per cent compared with 9 per cent for lesser margins ($P < 0{\cdot}01$) (*Figure 3*). The proportional hazard of survival was 0·48 (95 per cent c.i. 0·29–0·81) if the resection margin was $\leqslant 5$ mm compared with a margin >5 mm.

Asymptomatic patients had a better survival rate than symptomatic patients ($P < 0{\cdot}05$) (*Table 4*). Only 14 patients presented with symptoms from liver metastases (abdominal pain in 11, and fever, weight loss and malaise in three patients). Hepatic metastases were discovered during investigation or at operation for the primary tumour in 33 patients. Unsuspected hepatic metastases were discovered in three patients undergoing incidental laparotomy. Routine follow-up of patients with colorectal cancer disclosed hepatic metastases on investigation of a raised carcinoembryonic antigen (CEA) level (37 patients), abnormal liver function test results (five), routine radionuclide scintigraphy or ultrasonographic liver scan (ten), or hepatomegaly discovered on routine clinical examination (two).

Women had a survival advantage over men ($P = 0{\cdot}06$). The survival rate of patients with poorly differentiated primary tumours was nil at 3 years *versus* a 5-year survival rate of 20 per cent for patients with well or moderately differentiated tumours. These differences failed to reach statistical significance because of the small numbers of patients with poorly differentiated primary tumours (*Table 4*).

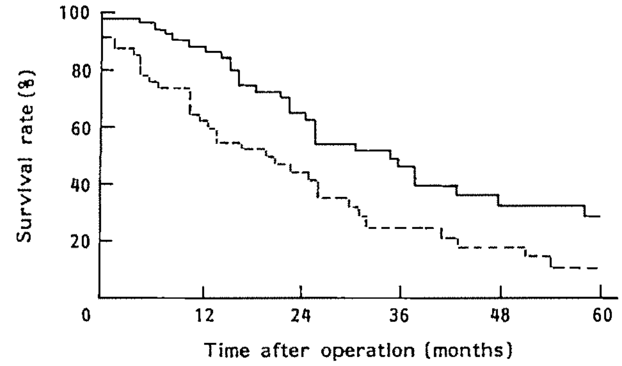
Hepatocellular carcinoma

The overall median survival of patients who had undergone resection of HCC was 12 months, and the 5-year survival rate 25 per cent (*Table 5*). There were no differences in survival rates between patients operated on before or after 1980.

Hepatectomy for HCC was classified as non-curative in 27 patients: 15 showed involvement of the resection margin on histopathological examination, five showed the presence of gross residual disease, three exhibited direct invasion of adjacent structures, and regional lymph node involvement was present in four. Curative operations were associated with a 44 per cent 5-year survival rate compared with 8 per cent for non-curative operations ($P < 0{\cdot}001$) (*Figure 4*). Only nine patients had a resection margin >5 mm; their 5-year survival rate was 40 per cent compared with a 17 per cent survival rate for patients with a margin $\leqslant 5$ mm (*P* not significant). However, if patients who had undergone non-curative operations were excluded, the 5-year survival rate was 54 per cent if the margin of resection was >5 mm *versus* 43 per cent for patients with a lesser margin (*P* not significant)

Preoperative α-fetoprotein estimation was performed for 25 patients. The median serum level was 19 ng/ml (range 9–447984 ng/ml; normal $<12{\cdot}5$ ng/ml). Patients whose preoperative estimation was within the normal range had a 37 per cent 5-year survival rate compared with none of the patients with high levels ($P < 0{\cdot}01$) (*Figure 5*). The odds ratio for survival was 0·26 (95 per cent c.i. 0·11–0·68) for patients with high α-fetoprotein levels

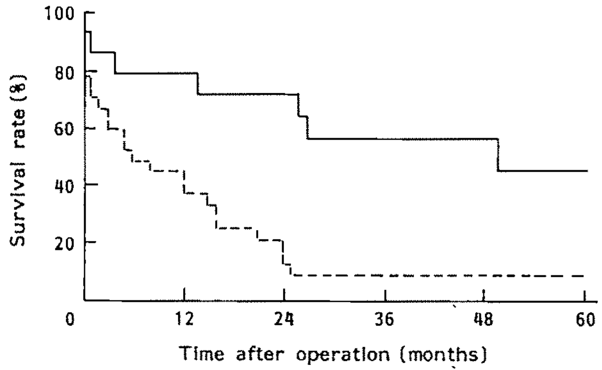
There was no significant difference in the survival rate between patients who were symptomatic and those who were not (*Table 5*). HCC was an incidental finding in seven patients, the diagnosis was made at incidental laparotomy in three Thirty-five patients were symptomatic· pain was the presenting complaint for 16, six discovered a mass, one had jaundice, six had malaise, fever and weight loss, and six underwent emergency resection for ruptured HCC



No. at risk

	0	12	24	36	48	60
Margin > 0·5 cm	51	43	25	17	8	7
Margin ≤ 0·5 cm	46	27	17	8	6	3

Figure 3 *Survival curves for patients who underwent hepatic resection for metastases from colorectal cancer with a resection margin* >5 *mm* (——) *and* $\leqslant 5$ *mm* (– – –). $P < 0.01$ (*log rank test*)



No. at risk

	0	12	24	36	48	60
Curative	15	12	10	7	6	4
Non-curative	27	12	5	3	3	3

Figure 4 *Survival curves for patients with hepatocellular carcinoma undergoing curative* (——) *and non-curative* (– – –) *resection* $P < 0.005$ (*log rank test*)

Table 4 *Survival rate following resection of liver metastases from colorectal cancer*

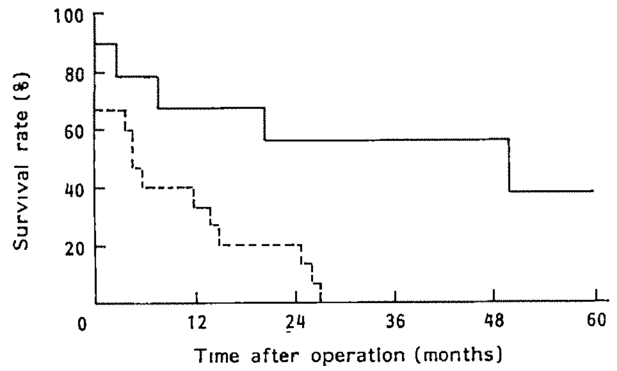
	No. of patients	Median survival (months)	Survival rate (%)			P*	Odds ratio (95% c.i.)
			1 year	3 years	5 years		
All patients	104	25	76	36	18		
Resection before 1980	12	32	67	42	17	0·966	0·98 (0·51–1·89)
Resection after 1980	92	26	78	34	19		
Colonic primary	60	26	78	39	19	0·774	0·93 (0·58–1·50)
Rectal primary	44	25	74	30	17		
Dukes' B	37	25	76	31	22	0·959	1·01 (0·61–1·68)
Dukes' C	54	26	75	39	16		
Well or moderate differentiation	77	25	80	36	20	0·168	0·50 (0·19–1·35)
Poor histological differentiation	9	11	56	0	0		
Primary to liver resection ⩽2 years	59	26	75	44	23	0·157	0·68 (0·40–1·16)
Primary to liver resection >2 years	37	24	78	20	10		
Synchronous disease	33	43	75	58	25	0·113	0·67 (0·41–1·10)
Metachronous disease	71	23	77	25	16		
Asymptomatic patients	90	26	81	38	19	0·043	0·42 (0·18–0·97)
Symptomatic patients	14	11	47	14	14		
Normal CEA	19	25	61	33	22	0·479	0·78 (0·40–1·53)
Raised CEA	62	24	87	31	18		
Female	51	31	84	42	24	0·058	0·64 (0·39–1·02)
Male	53	23	71	30	13		
Solitary metastasis	57	31	78	41	22	0·168	0·71 (0·43–1·15)
Multiple metastases	47	17	76	31	13		
No. of metastases							
1–3	87	26	79	36	19	0·343	0·70 (0·34–1·46)
⩾4	17	13	62	28	14		
Size of metastases							
⩽5 cm	52	26	84	41	22	0·058	0·60 (0·36–1·01)
>5 cm	43	24	66	31	9		
Curative resection	76	30	80	42	23	0·010	0·43 (0·23–0·82)
Non-curative resection	28	21	66	17	0		
Resection margin >5 mm	51	35	88	46	27	0·006	0·48 (0·29–0·81)
Resection margin ⩽5 mm	46	20	62	24	9		

CEA, carcinoembryonic antigen, c.i., confidence interval. *Log rank test

Table 5 *Survival rate following resection of hepatocellular carcinoma*

	No. of patients	Median survival (months)	Survival rate (%)			P*	Odds ratio (95% c.i.)
			1 year	3 years	5 years		
All patients	42	12	51	25	25		
Resection before 1980	14	24	64	28	28	0·168	0·60 (0·29–1·23)
Resection after 1980	28	8	41	23	15		
Male	20	12	48	42	31	0·527	0·80 (0·40–1·60)
Female	22	16	54	14	14		
Symptomatic patients	35	14	50	24	19	0·479	1·37 (0·58–3·24)
Asymptomatic patients	7	24	57	28	28		
Normal α-fetoprotein	10	50	67	56	37	0·005	0·26 (0·11–0·68)
Raised α-fetoprotein	15	5	33	0	0		
Patients without cirrhosis	33	16	54	26	22	0·168	0·49 (0·17–1·36)
Patients with cirrhosis	9	6	38	19	0		
Solitary tumour	22	15	50	31	23	0·764	0·90 (0·45–1·81)
Multifocal tumour	20	14	53	18	18		
Tumour size ⩽5 cm	10	24	60	25	25	0·601	0·81 (0·36–1·78)
Tumour size >5 cm	32	12	48	24	19		
Curative resection	15	50	79	56	44	0·001	0·30 (0·15–0·62)
Non-curative resection	27	6	37	8	8		
Resection margin >5 mm	9	27	67	40	40	0·180	0·58 (0·26–1·28)
Resection margin ⩽5 mm	33	12	47	20	17		

c.i., Confidence interval. *Log rank test



No. at risk						
α-fetoprotein ≤12 ng/ml	10	7	6	5	4	2
α-fetoprotein >12 ng/ml	15	6	4			

Figure 5 *Survival curves for patients with resected hepatocellular carcinoma with preoperative α-fetoprotein level ≤12 ng/ml (——) and >12 ng/ml (----).* P < 0·01 (*log rank test*)

Cholangiocarcinoma

Hepatic resection was performed for five patients with hilar cholangiocarcinoma, three with peripheral cholangiocarcinoma and four with carcinoma of the gallbladder involving the fossa. The median survival of this group of patients was 10 months; one patient survived to 5 years (5-year survival rate 22 per cent). Although the small number of patients in this group precluded life-table analysis of subgroups, the three patients with peripheral cholangiocarcinoma all died within 12 months while all four with hilar cholangiocarcinoma who survived the operation were alive at 14 months. All patients with carcinoma of the gallbladder died within 2 years, three within the first year.

Hepatic sarcoma

Histopathological examination of the 11 patients with hepatic sarcoma showed leiomyosarcoma (five patients), fibrosarcoma (two), malignant histiocytoma (one), malignant schwannoma (one), lymphoma (one) and undifferentiated sarcoma (one). The tumour originated in the liver in six patients and metastasized to the liver from the stomach (two), retroperitoneum (two) and ileum (one) in five. One of the 11 patients was alive at 5 years (5-year survival rate 25 per cent).

Three children underwent resection of a hepatoblastoma. Although two were alive and well at 55 and 150 months after operation, the third had recurrent disease at 39 months.

Discussion

This study examines whether it is possible to improve the long-term survival rates of patients with hepatic malignancy by defining criteria for the selection of patients for hepatic resection. While the operative mortality rate for hepatic resection has fallen in recent years[1], the present data show no improvement in the overall 5-year survival rate.

Resection of metastases from colorectal cancer

The efficacy of resection of liver metastases from tumours of the colon and rectum has recently been questioned[7] In previous studies, the 5-year survival rate after resection of hepatic metastases[8–16] has been between 10 and 34 per cent, which is consistent with the present data. The survival of patients with untreated metastases to the liver from primary tumours of the colon and rectum[17–23] is between 5·6 and 13 months. However, patients with multiple, but potentially resectable, metastases survive a mean of 10·6 months, and those with solitary hepatic metastases[24] survive 16·7 months. There are no controlled trials comparing hepatic resection with non-surgical management for potentially resectable hepatic metastases. None the less, patients in this series who had undergone hepatic resection for metastases had a better survival rate than historical patients treated without operation[12,25,26].

The histological grade of the primary tumour may be important in the selection of patients for resection of liver metastases Few patients with poorly differentiated primary neoplasms underwent resection of liver metastases; therefore the worse survival of patients with poorly differentiated tumours compared with those with moderately or well differentiated tumours failed to reach statistical significance. The present data accord with a previous report showing a mean survival of 7·1 months for patients with resected metastases from poorly differentiated tumours compared with 17·9 months for those with resected metastases from moderately or well differentiated tumours[27], and suggest that patients with metastases from poorly differentiated tumours may not benefit from hepatic resection.

Consistent with other reports, the present data show that the Dukes' classification of the primary cancer is not important in the selection of patients for resection of hepatic metastases[10,28–32]. Other groups, however, have reported 5-year survival rates between 7 and 45 per cent higher after resection of hepatic metastases from Dukes' B compared with Dukes' C lesions[15,16,33–35]. None the less, the difference in survival rate was insufficient to deny patients with Dukes' C primary tumours the potential for cure.

The interval between resection of the primary tumour and resection of hepatic metastases is not important in the selection of patients for resection of colorectal liver metastases. The present data show a trend towards a better survival rate if this interval is ≤2 years, and for patients who have undergone resection of metastases discovered during surgery for the primary tumour. However, the improved survival rate of patients with synchronous metastases, or of those whose close follow-up resulted in the early detection of metastases, may represent a lead-time bias Others[36,37] have reported a longer median survival for patients with synchronous metastases of between 4 and 9 months and a 66 per cent 5-year survival rate for patients with synchronous metastases compared with zero for patients with metachronous metastases[11]. Conversely, others have reported a 5-year survival rate between 10 and 26 per cent better for patients with metachronous metastases[38,39]. An improved 5-year survival rate of 40 per cent for patients with a disease-free interval > 1 year, compared with 28 per cent for a shorter disease-free interval, has also been reported[15], possibly reflecting a lower biological activity of tumours showing a long disease-free interval. However, most studies have shown no significant differences in the survival rate after resection of liver metastases when analysed according to the interval between resection of the primary and the discovery of hepatic metastases[8,10,16,28,29,40–43], further, this interval is of no account in the selection of patients for hepatic resection or in the determination of prognosis.

The presence of symptoms from hepatic metastases may not be a contraindication to resection The present data agree with those from a multicentre study that reported a 32 per cent 5-year survival rate for patients with symptoms from hepatic metastases compared with 45 per cent when metastases were discovered on routine follow-up or investigation[34]. Because symptomatic metastases may be considered to be at a later stage in their growth, a lead-time bias may account for the better survival of patients with asymptomatic metastases.

The findings at operation are of great importance in determining the prognosis after resection of metastases from colorectal cancer. The present data confirm a previous report[15] that non-curative resection of liver metastases is associated with a 5-year survival rate of less than 5 per cent. The presence of neoplasia at the resection margin[15,27,29] and of margins of at least 5 mm (Reference 44), 10 mm (References 9, 15, 34) and 20 mm (Reference 45) have been analysed with respect to the long-term survival rate. These reports support the present data, which show a significantly improved 5-year survival rate for patients with a margin of resection of >5 mm. These data also show the futility of resection of metastases in the presence of lymphatic involvement regional to the hepatic metastases, extrahepatic spread or in circumstances resulting in gross residual disease after resection.

The number of metastases may not be relevant in the selection of patients for hepatic resection, provided that there is no extrahepatic spread and an adequate margin of resection can be achieved. These data support previous reports showing no worse survival in patients with multiple metastases[10,16,33,36]. Other reports have suggested that the survival rate is better following resection of solitary metastases[9,15,27,29,30,34,37,41,42,46]. No discrimination was made in the present study between multifocal and solitary metastases with satellite lesions. One study, however, reported that satellite lesions around solitary metastases do not affect prognosis[42], while another showed a worse prognosis with satellite lesions[9].

Resection of metastases from other primary sites

Although no significant differences were found when patients with metastases from sites other than the colorectum were compared with those undergoing resection of metastases from the colorectum, the histology of the primary tumour was important in determining the prognosis. Of the five surviving patients, two with slowly growing metastases from ileal carcinoid tumours who underwent palliative resection are alive in addition to three with gynaecological or breast carcinomas. Patients with metastases from carcinoma of the stomach and pancreas fared badly. Other reports with similar results[13,46] also do not recommend resection of metastases from primary sites other than the colorectum with intent to cure, although palliative resection may be indicated for metastases from some tumours, for example ileal carcinoid tumours and those from rare sites such as mesonephric duct carcinoma.

Primary liver tumours

Patients with untreated HCC survive between 1 and 4 months after diagnosis[47–52]. Those fit enough to undergo palliative surgery survive between 7 (References 48, 53) and 10·8 (Reference 50) months while patients undergoing curative resections survive between 23 (Reference 53) and 42 (Reference 50) months. In selected patients, surgical resection is superior to systemic or regional chemotherapy[48,49,51,54], radiotherapy[51,54], or hepatic artery ligation or dearterialization[48,54] The poor results of non-surgical therapy support the case for surgery despite the higher operative risk of resection for HCC than for metastatic liver disease[1].

The α-fetoprotein level may be useful in the preoperative selection of patients for hepatic resection for HCC The present data show a worse survival rate for patients with a raised level of α-fetoprotein before operation One report[55] has shown a median disease-free survival of 531 days for patients whose α-fetoprotein level was <200 ng/ml compared with 176 days for those with a level >200 ng/ml, and a second study has confirmed this better survival[56].

The feasibility of performing a curative resection is most relevant in the selection of patients for resection of HCC. The present data agree with a previous study[57] which reported a 70 per cent 5-year survival rate for those undergoing curative resection but no survivors amongst patients undergoing palliative resection, defined as the absence of a capsule around the tumour, the presence of satellite lesions, the presence of vascular or bile duct invasion, or a margin of resection <10 mm. Similarly, other studies have reported a 50 per cent 5-year survival rate in the absence of extrahepatic spread compared with no 5-year survivors among patients with a locally invasive tumour[58], and a 75 per cent 5-year survival rate for patients with completely resected tumours compared with 11 per cent for those whose tumours had spread locally or to distant sites[59].

However, the present data also suggest that the margin of resection *per se* is not important in the prognosis of HCC. The 5-year survival rate was similar for patients undergoing curative resection whether or not the resection margin was >5 mm. Although one study has reported a 533-day disease-free survival for patients with a negative margin of resection *versus* 160 days when the margin was involved by tumour[55], another[60] has reported no significant difference in recurrence of tumour in the liver after limited resection with a resection margin <10 mm compared with patients whose tumours were resected with a margin >10 mm. Similarly, for patients with small HCC complicating cirrhosis, limited hepatic resection was associated with a trend towards better survival than for those undergoing major hepatic resection[61].

The median survival of patients with HCC complicating cirrhosis is 1·2 *versus* 13 months for those with HCC in non-cirrhotic liver[58] Increasing severity of cirrhosis, as defined by Pugh's modification of Child's classification, adversely influences both the operative mortality rate (3·7 per cent for Child's grade A, 16·7 per cent for grade B/C) and the long-term survival rate (56·7 per cent 5-year survival for Child's grade A, 12·2 per cent for grade B/C) of patients undergoing resection of HCC complicating cirrhosis[62]. The safe limits of hepatic resection are dependent not only on the volume of liver resected but also on preoperative liver function[47,63]. None the less, one report showed no statistical difference in the survival rates of patients undergoing resection of HCC from a cirrhotic liver compared with those without cirrhosis[56]. However, 58 per cent of the patients with HCC in a cirrhotic liver underwent minor resection compared with 24 per cent of those without cirrhosis Only nine of the present patients with HCC had cirrhosis; the trend towards worse survival in these patients was not statistically significant.

These data indicate that the selection of patients for resection of primary and secondary liver tumours may improve survival. The major contraindications to resection are finding that a tumour has extrahepatic spread or regional lymph node involvement, or both, or that it is not resectable without leaving gross residual neoplasia. For metastases from colorectal cancer, the margin of resection and possibly the histological grade of the tumour are important For HCC an α-fetoprotein level >12·5 ng/ml may be a contraindication to resection

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Perineal trauma from cassette tape boxes

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Two vehicles collided at an impact speed in excess of 160 m.p h All three occupants of one car sustained a perineal injury. We believe that the injuries were caused by the plastic boxes in which cassette tapes are stored

Case reports

Patient 1

A 22-year-old woman was retrieved unconscious from the car. She had sustained both a serious head injury and a perineal injury. She had a large perineal haematoma with a central laceration without rectal or vaginal involvement This injury was managed conservatively and healed without incident

Patient 2

A 24-year-old man was rescued from the back seat of the car. He had originally been sitting in the front passenger seat wearing a seatbelt His injuries included a right-sided pneumothorax and a stable undisplaced crush fracture of the third lumbar vertebra

He had also sustained a major perineal injury involving the anus After resuscitation, formal examination under anaesthesia revealed a complete disruption of the internal and external anal sphincters with the wound extending anterolaterally into the perineum. There was a minor split posteriorly The injury was deep and extended to the ischial tuberosity on the right side

Primary repair of the sphincter was effected with interrupted mattress sutures of chromic catgut (*Figure 1*) The remaining perineal defect was packed with flavine gauze, and faecal diversion was achieved with a defunctioning left iliac fossa loop colostomy Ten days after the initial injury, rectal examination revealed voluntary anal sphincter contraction The patient was discharged from hospital to undergo a formal test of anal function 3 months later and closure of colostomy thereafter provided continence is satisfactory.

Patient 3

The driver of the vehicle, a 25-year-old man, was found to have sustained severe lacerations, a fracture dislocation of the left hip and a right olecranon fracture He had also sustained an injury to the perineum giving severe contusion to the base of the penis without laceration The latter injury required no intervention.

Discussion

The original theory as to the cause of these unusual injuries was that the seat springs had been forced through the seat covers into the perineum of the occupants of the car. However, a detailed police inspection showed that the seats had not been damaged in this way. The car did, however, contain many fragments of plastic derived from the covers of cassette tape boxes. The fire officer who extracted patient 2 from the car then reported that he had removed an arrow-shaped piece of plastic from the perineal wound of this patient.

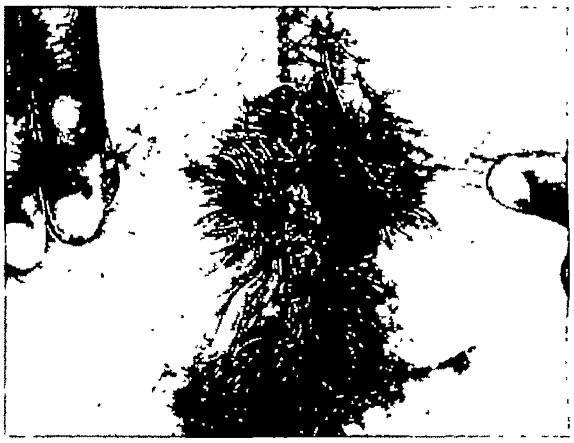

Figure 1 *Anal sphincter disruption after repair in patient 2*

When these plastic fragments are examined it becomes apparent that they are capable of causing incised wounds, and we suggest that they were indeed the cause of the three perineal injuries sustained in this accident. A literature search and inquiries of the Police Transport and Road Research Laboratories have not revealed reports of any other similar injuries. Beard *et al.*[1] reported six severe pelvic injuries associated with traumatic abduction of the leg, but all were associated with a pelvic fracture which was not the case in any of the present patients

The sequence of events in the maelstrom of a 160-m.p.h. deceleration can only be guessed at. We suggest that the occupants were first thrown forwards on to their seatbelts (phase 1), and were also tipped forwards, elevating the perineum. They were then thrown backwards (phase 2), into the path of the cassette tape boxes which were moving forwards. The most serious perineal wound occurred in the patient who came to rest (phase 3) in the rear of the vehicle having been travelling in the front passenger seat. Given that the plastic shard retrieved from the perineum of patient 2 did not appear to be part of a whole box that had been sat on and splintered, we suggest that the injuries occurred between phases 2 and 3 when the patients and missiles were travelling in opposite directions.

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Encephalopathy in patients with extrahepatic obstruction after lienorenal shunts

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Thirty patients with portal hypertension resulting from extrahepatic portal vein obstruction were studied. Evidence of postshunt encephalopathy was sought using neurological and psychometric tests and visual evoked potentials. Eleven patients were studied before and after lienorenal shunt operations and 19 at varying intervals, from 6 to 123 (median 26) months, after the same procedure. All the shunts were patent and none of the patients developed clinical or subclinical encephalopathy. In patients with extrahepatic portal vein obstruction, a lienorenal shunt does not appear to be associated with postshunt encephalopathy.

The incidence of encephalopathy after portosystemic shunting in patients with portal hypertension resulting from extrahepatic portal vein obstruction (EHPVO) has been variously reported to be between zero[1,2] and 35 per cent[3]. The reports of a high incidence have been from Western countries where the mean age of the patients has been higher[3] than in India[4] and where encephalopathy has been defined to include patients needing a psychiatric consultation[5]. EHPVO is uncommon in the West and the disorder occurs in only 5–10 per cent of all patients with portal hypertension[6].

In India, however, EHPVO is a common cause of portal hypertension and occurs in young patients (mean age 20 years)[4]. A well performed lienorenal shunt is an effective procedure to prevent rebleeding[4], which is the main cause of death. It was thus important to determine whether, in preventing death from rebleeding in patients with EHPVO, there might be an increased risk of death from postshunt encephalopathy and liver failure, as is often the case with patients with cirrhosis who have undergone portosystemic shunting[7].

A systematic study was therefore carried out to determine the incidence of encephalopathy in patients with EHPVO who had patent lienorenal shunts. Encephalopathy was assessed objectively with neurological tests for clinical and subclinical encephalopathy and for changes in visual evoked potential (VEP).

Patients and methods

Two groups of patients were tested: group 1 consisted of 11 patients tested both before and after lienorenal shunting while group 2 was made up of 19 patients tested at varying periods after they had undergone a lienorenal shunt. All the patients studied had patent shunts demonstrated by ultrasonography and a two-grade reduction in variceal size revealed on endoscopy[8].

Group 1 patients

Between October 1988 and November 1989, 35 patients with EHPVO underwent operation, of whom 26 had end-to-side lienorenal shunts. Patients below 10 years of age ($n = 10$) and illiterates ($n = 4$) were excluded from the study as they could not complete the psychometric tests. One patient who underwent the preoperative tests was lost to follow-up. The remaining 11 were tested before and between 3 and 15 (median 6) months after operation. Control subjects ($n = 11$) were the relatives of other patients admitted to the ward who did not have liver disease. Controls were matched for age, sex and education with the study group.

Group 2 patients

Patients with EHPVO who had previously undergone a lienorenal shunt and who attended the portal hypertension follow-up clinic between October 1988 and November 1989 were tested for encephalopathy. They were included in the study if they were >10 years old and literate.

The 19 patients in this group were tested between 6 and 123 (median 26) months after operation. They were compared with an equal number of control subjects who did not have liver disease and who were matched for age, sex and education.

Informed consent was obtained from patients before the tests were performed.

Tests for encephalopathy

Patients and control subjects underwent a detailed neurological examination with assessment of higher mental function.

Psychometric tests were carried out in a quiet room by one of the investigators and consisted of:

1. The number connection test, using standard charts (Duphar, Southampton, UK) with the Roman numerals substituted by Devanagari ones. The time in seconds taken to complete the test was recorded.
2. Construction of a five-pointed star, using the scoring system followed by Zeegen *et al.*[9], which takes into account the number of sharp points drawn, inner angles replicated and the relative length of the lines. The error score was then calculated.
3. The reverse counting test, i.e. the time taken to count from 100 to 50 (in the mother tongue). The number of errors made was recorded.

The VEP was measured using the Nicholet Compact Four model (Nicholet, Madison, Wisconsin, USA). Each eye was tested separately using the chequerboard pattern as the source stimulus. Scalp electrodes were placed according to the 10–20 system. The recording electrode was placed in the parieto-occipital region over the midline and the reference electrode on the forehead. A total of 500 stimuli were averaged to obtain the final recording of the P100 (P1) wave. At least two readings were taken from each eye to determine the consistency of the wave formation. The absolute latency of the P100 wave was measured. The calculated normal value of more than 3 s.d. (1 s.d. is 4·32 ms) was considered to be significant (upper limit 110 ms).

Statistical analysis

Differences between the psychometric test results before and after operation were compared using the Wilcoxon signed rank test, and those between the patients and controls with the Wilcoxon non-parametric test for independent samples with correction for bias. The differences between the results of the VEPs were compared using Student's *t* test. An individual result was judged to be abnormal if it lay 2 s.d. above or below the mean obtained from matched healthy controls.

Results

In group 1 there were eight male patients and three female whose ages ranged from 12 to 28 (median 16) years. Group 2 had 14 male patients and five female whose ages ranged from 10 to 45 (median 24) years. Detailed neurological examination

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Table 1 *Results of psychometric tests in group 1 and group 2 patients*

	Group 1 (*n* = 11)			Group 2 (*n* = 19)	
Test	Before operation	After operation	Controls	Patients	Controls
Number connection test (s)	67·7(33·7)	61·5(30·4)	63·8(27·8)	65·8(25·7)	63·7(22·8)
Five-pointed star construction (no. of errors)	4·1(3·1)	3·3(2·2)	3·6(1·6)	3·8(1·7)	3·5(1·2)
Reverse counting					
Time (s)	56·2(26·9)	42·9(14·4)	49·1(17·4)	53·6(25·4)	52·4(21·2)
Error score	1·7(2·8)	1·5(2·3)	1·6(1·7)	3·6(4·1)	3·2(3·1)

Values are mean(s.d.)

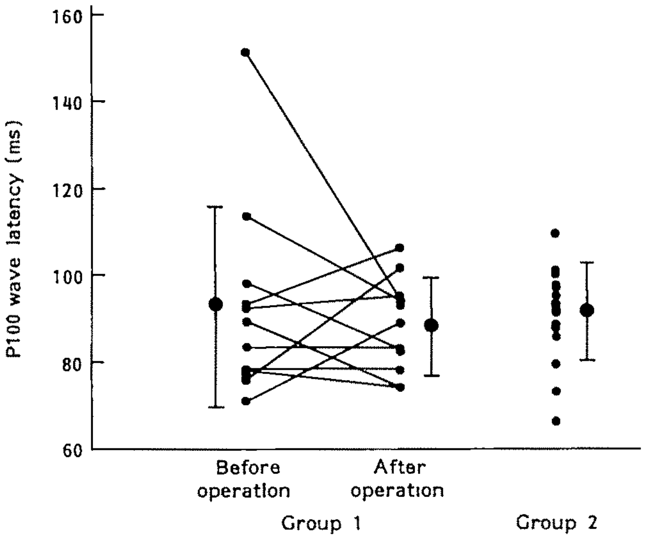

Figure 1 *Visual evoked potentials (latency of P100 wave) in group 1 and group 2 patients. Bars are mean(s.d.)*

and assessment of higher mental function showed no abnormalities in either group.

Psychometric tests (Table 1)

In group 1, patients took about the same time to complete the number connection test before and after surgery as control subjects. Error scores were also similar. Patients in group 2 and their controls also had near-identical scores.

The mean error score for construction of a five-pointed star in the patients in group 1 was similar before and after surgery and was not different from that of control subjects. Patients in group 2 and their controls also had nearly identical error scores.

The results of the reverse counting test were similar when the patients were tested before and soon after operation or at varying intervals afterwards. There were no significant differences in results between the patients and controls.

Visual evoked potential (Figure 1)

The mean(s.d.) latencies of the P100 wave before operation in group 1 were: right eye 93(23) ms and left eye 92(23) ms. After operation they were: right eye 88(12) ms and left eye 88(10) ms. These differences were not significant. Two patients had abnormal latencies in both eyes before operation which became normal after surgery.

In group 2 the mean(s.d.) latency of the P100 wave for the right eye was 89(10) ms and for the left eye 94(12) ms; all the results fell within the normal range.

Discussion

The results indicate that a lienorenal shunt operation for patients with EHPVO is not followed by either clinical or subclinical portosystemic encephalopathy. Previous reports of a high incidence of this complication were obtained in studies on much older patients, many of whom had compromised liver function (35 per cent of patients in one study had ascites) and EHPVO secondary to other diseases[3]. The study by Voorhees *et al.*[5] reported a high incidence of postoperative encephalopathy but included children who needed a psychiatric consultation; some patients who had undergone oesophagectomy without a portosystemic shunt had evidence of encephalopathy. In contrast, other reports[1,2,10–12] have found no clinical evidence of encephalopathy in patients followed for up to 10 years, and Alagille *et al.*[13] reported no loss of intellectual and psychological capacity on psychometric testing in 42 children followed for up to 24 years. These differences in encephalopathy rates are probably caused by inclusion in some series of patients with EHPVO secondary to other disorders and by an improper definition of encephalopathy.

This study was designed to detect very minor degrees of brain dysfunction by using psychometric tests and VEPs, and by studying one group of patients before and after operation and the other for varying intervals afterwards. No evidence was found of clinical or subclinical encephalopathy after lienorenal shunt in patients with EHPVO.

The present results have major implications for the management of these patients. EHPVO is a common cause of portal hypertension in India[14] and a well performed lienorenal shunt effectively reduces the likelihood of rebleeding[1,2,4], the major cause of death in these patients. If there is no postshunt encephalopathy (in contrast to patients with cirrhosis) then patients with EHPVO may be restored to a life of almost normal quality and span. Lienorenal shunting is a single and curative procedure and particularly suitable for a poor patient in India who may live far from a medical centre that can deal with such a complex problem. Alternative treatments such as endoscopic sclerotherapy and propranolol require repeated hospital visits, close and careful monitoring, and have rebleeding rates in EHPVO higher than for well performed shunt operations. No case of overwhelming postsplenectomy sepsis in either adults or children was encountered in the present study, nor by paediatric surgical colleagues (unpublished observations). Indian patients seem to be resistant to this complication.

It is suggested, therefore, that lienorenal shunting is an effective mode of treatment for patients with EHPVO and is, at least in the short term, not followed by postshunt encephalopathy.

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Case report

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Acute right iliac fossa pain in pregnancy: the role of fine-catheter peritoneal cytology

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The diagnosis of acute appendicitis in pregnancy can be difficult. The cases are reported of two pregnant women with suspected acute appendicitis whose management was greatly influenced by the use of fine-catheter peritoneal cytology (FCPC)

Case reports

Patient 1

A 28-year-old woman in the 32nd week of her third pregnancy presented with a 10-h history of increasingly severe abdominal pain that originated in the epigastrium and shifted to the right side of the abdomen The patient was nauseated, had passed one loose stool and had no urinary symptoms. On examination she looked unwell, with a temperature of 37·1°C and a strong fetor oris Abdominal palpation revealed a longitudinal-lying fetus and marked tenderness with guarding and rebound over the right lateral mid-abdomen. The white cell count was $7{\cdot}8 \times 10^9$/l with no granulocytosis. Examination of the urine was negative. Ultrasonography demonstrated a right anterior placenta with no sign of abruption.

FCPC was performed as previously described[1]. Briefly, under sterile conditions, an intravenous cannula was inserted through the abdominal wall and an umbilical catheter was passed through the sheath into the peritoneal cavity In this instance the cannula was introduced over the area of maximal tenderness and lateral to the uterus. The catheter was manipulated in the direction of maximal tenderness while negative pressure was applied with a 10-ml syringe. A smear of the aspirate was stained using the modified Romanovsky method, and the percentage of nucleated cells that were neutrophils was assessed. This result was 10 per cent (negative), >50 per cent being regarded as positive[2], and so a decision to observe the patient was made. Over the next 24 h, the pain subsided and the patient was discharged. At 41 weeks she delivered a healthy female baby

Patient 2

A 22-year-old woman in the 18th week of her third pregnancy presented with a 20-h history of right-sided abdominal pain that was sharp, constant and did not radiate. She was nauseated and had vomited once. The patient had frequency of micturition but no dysuria On examination she was pale, with a temperature of 37·2°C. Abdominal palpation revealed a pregnant uterus and marked tenderness with guarding in the right iliac fossa. The white cell count was $14{\cdot}3 \times 10^9$/l. Examination of the urine was negative. Ultrasonography demonstrated a normal pregnancy and no abnormality

FCPC was performed and the result was 10 per cent (negative) A decision to observe the patient was made. After 24 h, the pain had resolved and the patient was discharged. At 39 weeks she delivered a healthy male baby

Discussion

FCPC has been shown to be a safe and useful adjunct to decision making in patients with acute abdominal pain[1,2] and has helped to reduce the negative appendicectomy rate[3]. An alternative strategy is to observe these patients carefully, but any delay in operating carries risks, particularly in pregnancy, where there is a higher proportion of perforated appendicitis with its associated increase in maternal and fetal mortality rates[4,5].

Conversely, a policy of early surgical intervention, to reduce the number of maternal and fetal complications, results in unnecessary appendicectomy rates[4,5] of 17–36 per cent and an increased fetal morbidity rate[5]. Unnecessary appendicectomies were avoided in the two women reported here, and we recommend that FCPC be considered as part of the investigation of pregnant patients with suspected appendicitis.

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Physiological variation in rectal compliance

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The volume (V) *of air inflated in a latex balloon placed in the rectum and the corresponding pressures* (P) *were measured in 48 subjects* (*24 men and 24 women*) *at three points:* (*1*) *earliest defaecation urge;* (*2*) *constant defaecation urge; and* (*3*) *maximum tolerable volume* (*MTV*). *The rectal pressures in all three cases were higher in men than in women. Woman aged over 60 years had higher rectal compliance* ($\Delta V/\Delta P$) *than men in the same age group, while no difference was found between men and women below the age of 60 years. Day-to-day variation of the measurements was tested in ten subjects. Reproducibility was good only for MTV* (*95 per cent confidence interval 57–183 per cent*). *Reproducibility of rectal compliance decreased with increasing values for this parameter. No such trend was found for the other parameters. In conclusion, MTV is a reproducible parameter and suitable for clinical use in evaluation of patients with faecal incontinence or constipation.*

Rectal distension is used to measure rectal sensation and compliance[1,2]. Abnormal rectal compliance and volume tolerability have been demonstrated both in patients with faecal incontinence and those with constipation[3–5]. Variation in anal pressure with age and sex are well documented[1,6–8]. Studies on rectal compliance and volume tolerability have concentrated on age differences[1,6,9,10] while sex differences have gained little interest[7]. The aim of the present study was to investigate the influence of age, sex and day-to-day variation on rectal compliance and volume tolerability

Subjects and methods

Forty-eight healthy volunteers (24 women and 24 men) with no history of anorectal dysfunction participated in the study The median age for men was 54 (range 24–80) years and for women 53 (range 25–78) years A latex balloon measuring 5 × 3 cm when deflated was placed in the rectum with its centre 10 cm from the anal verge A pressure probe was placed between the balloon and the rectal wall with the end of the probe situated at the middle of the balloon (*Figure 1*) The pressure recording system used consisted of a low-compliance open-ended perfused polyvinyl catheter connected to a strain gauge and displayed on a chart recorder, as described previously[3] The rectal balloon was distended by continuous inflation with air at a rate of 75 ml/min The subjects were instructed to report when they experienced (1) earliest defaecation urge (EDU); (2) constant defaecation urge (CDU); and (3) maximum tolerable volume (MTV), which resulted in an irresistible or painful urge to defaecate. The rectal volumes and corresponding pressures were recorded at each sensation Rectal compliance was calculated from the volume and pressure increases measured from the start to MTV. In ten subjects the study was repeated on another day to evaluate day-to-day variation All were examined during the day and were not fasting. They were all invited to defaecate before the examination, but no bowel preparation was used No other means of standardization was attempted.

The Mann–Whitney *U* test for unpaired data was used for statistical analysis. Results are given as median (range). Day-to-day variation was evaluated by plotting data as described by Bland and Altman[11] and Murray and Miller[12] Reproducibility was expressed as the 95 per cent confidence interval for the variation

Results

Rectal volumes registered for each sensation did not differ significantly between men and women, irrespective of age (≤60 or >60 years), as shown in *Table 1*. Increase in rectal pressure was significantly higher in men for EDU, CDU and MTV. No overall significant difference in rectal compliance between men and women was demonstrated, but women >60 years of age had higher rectal compliance than men in the same age group. No correlation between volumes, rectal pressures or rectal compliance and age was found, although the inflated volumes of air at all three points tended to be lower in men >60 years old ($P = 0{\cdot}18$). Variation from day to day in rectal compliance (day 1/day 2) showed an increase with increasing compliance (*Figure 2*). The reproducibility of volumes and pressures at EDU, CDU and MTV is shown in *Figures 3, 4* and *5*. No systematic trend was found, indicating that the variation encountered was related to each individual rather than to the method. The 95 per cent confidence intervals for day-to-day variation of all parameters are shown in *Table 2*.

Discussion

In the present study a higher increase in rectal pressure was found in men during inflation of the rectal balloon, which is in contrast to other studies where no sex difference in rectal compliance has been found[4,6,7]. The sex difference could, however, be demonstrated only in those >60 years old. One

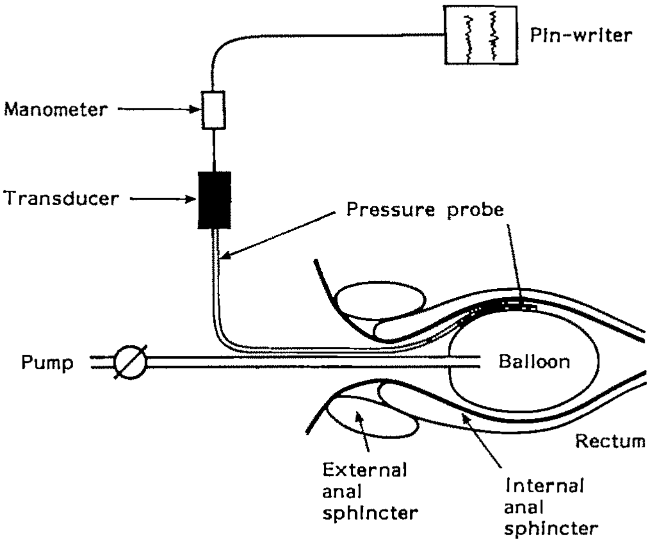

Figure 1 *Set-up for measurement of rectal compliance*

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Table 1 *Sex differences in volume inflated, rectal pressure and rectal compliance*

	Women			Men		
	⩽60 years ($n = 14$)	>60 years ($n = 10$)	Total ($n = 24$)	⩽60 years ($n = 13$)	>60 years ($n = 11$)	Total ($n = 24$)
Volume inflated (ml)						
EDU	85	90	87 (50–300)	160	111	117 (40–362)
CDU	155	150	155 (89–355)	205	167	189 (95–442)
MTV	220	210	220 (130–440)	330	220	245 (140–500)
Rectal pressure (mmHg)						
EDU	5‡	6‡	5 (0–18)†	10	10	10 (4–35)
CDU	10‡	11	10 (0–40)†	14	16	16 (6–42)
MTV	16	12‡	13 (4–46)†	20	20	20 (8–40)
Rectal compliance (ml/mmHg)*	18	17‡	17 (5–48)	14	9	14 (4–40)

Values are median (range). EDU, earliest defaecation urge; CDU, constant defaecation urge; MTV, maximum tolerable volume. *$\Delta V/\Delta P$. †$P < 0{\cdot}05$ (all women *versus* all men), ‡$P < 0{\cdot}05$ (women *versus* men of corresponding age), Mann–Whitney *U* test

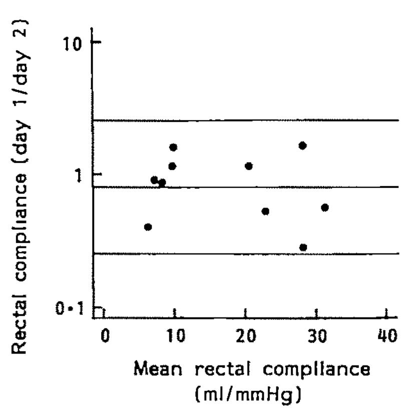

Figure 2 *Day-to-day variation in rectal compliance (day 1/day 2) in ten subjects. Mean and 95 per cent confidence interval are shown*

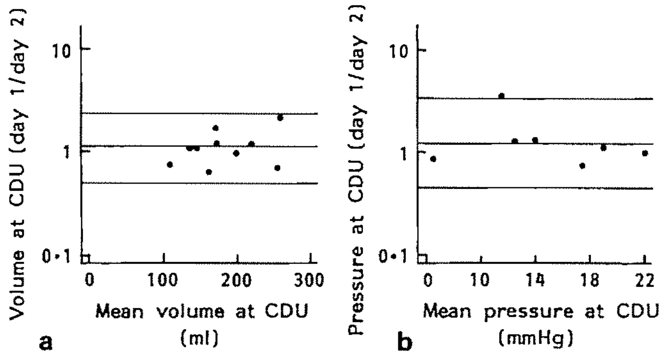

Figure 4 *Day-to-day variation in* **a** *rectal volume and* **b** *corresponding pressure (day 1/day 2) at constant defaecation urge (CDU). Mean and 95 per cent confidence interval are shown*

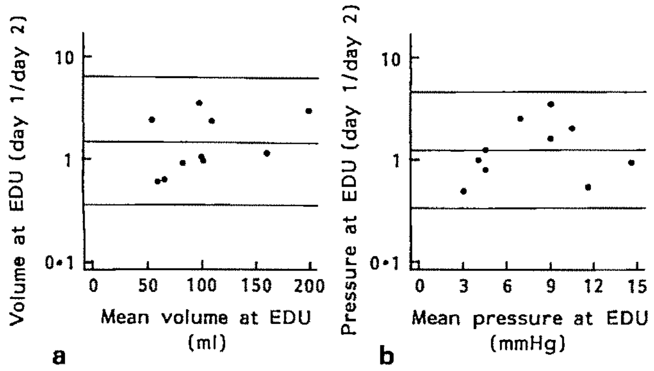

Figure 3 *Day-to-day variation in* **a** *rectal volume and* **b** *corresponding pressure (day 1/day 2) at earliest defaecation urge (EDU). Mean and 95 per cent confidence interval are shown*

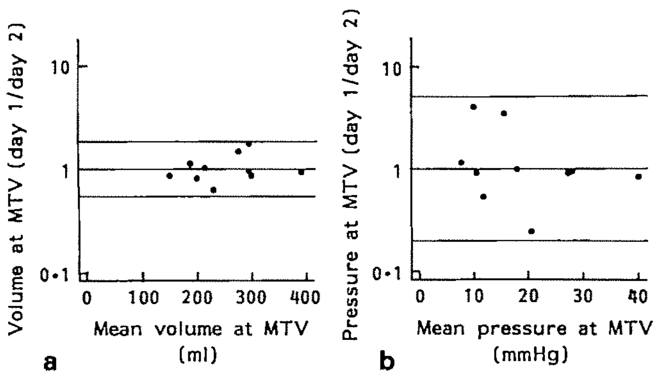

Figure 5 *Day-to-day variation in* **a** *rectal volume and* **b** *corresponding pressure (day 1/day 2) at maximum tolerable volume (MTV). Mean and 95 per cent confidence interval are shown*

previous study referred only to subjects <26 years old[4], and so a possible sex difference in older age groups would have been overlooked.

In the present study men also tended to have higher volumes at EDU, CDU and MTV than women, although not significantly so. This is in agreement with some studies[9,13] but in contrast to others[4,10]. Difference in methods[10] and in composition of control groups[4] may be an explanation of this discrepancy.

No significant decrease in MTV with age was demonstrated, although volumes at EDU, CDU and MTV tended to be lower in older men. With similar methods others have found MTV and volume at EDU to be lower in older subjects[14], and have

Table 2 *Reproducibility for rectal compliance and corresponding volumes and pressures at the three points studied*

	Volume (ml)	Pressure (mmHg)
EDU	38–499	35–426
CDU	51–231	45–310
MTV	57–183	21–502

Values are 95 per cent confidence intervals; rectal compliance was 25–252 per cent. EDU, earliest defaecation urge; CDU, constant defaecation urge, MTV, maximum tolerable volume suggested there is a less elastic ampulla in the elderly resulting from progressive fibrosis.

Reproducibility of the measurements was found to be acceptable only for MTV; considerable variation was present in the others. Since the measurements are linked to a subjective sensation in the rectum, and since no bowel preparation was used, faecal content in the rectal ampulla may influence the results. In spite of this, the method has been useful in the evaluation of patients with faecal incontinence[3]. Rectal compliance reproducibility decreased with increasing compliance, which is in accordance with a previous reproducibility study[15].

In conclusion, the MTV is a reproducible measurement that is suitable for clinical use in evaluating patients with faecal incontinence or constipation. The observed sex difference in pressure measurements should be taken into account in studies of rectal compliance.

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Paper accepted 20 March 1992

Erratum

Derodra JK, Reidy JF, Jourdan MH. Embolization of superior haemorrhoidal artery in the management of life-threatening rectal bleeding. *Br J Surg* 1992; **79**: 704–5.

Details of the main product used in the above Case Report were unfortunately inaccurate. The material mentioned (Gelfoam) is manufactured by Upjohn of Kalamazoo, Michigan, USA and currently without a product licence in the UK. The product used by the authors was actually Spongostan, which is made by Johnson and Johnson Medical of Ascot, UK.

Those submitting manuscripts are reminded that the Instructions to Authors require full and accurate product details. The authors apologize for any confusion caused in this case.

Correspondence

Anterior resection without a defunctioning colostomy: questions of safety

Letter 1

Sir

Mr Mealy and colleagues (*Br J Surg* 1992; 79 305–7) make a strong case for avoiding defunctioning stomas after anterior resection I am concerned, however, that we are not all talking the same language when referring to anterior resection or to mesorectal excision

Anterior restorative resection of the rectum is an operation usually performed for rectal cancer that traditionally is qualified as being high or low depending on the level of the anastomosis, this in turn depends on the site of the tumour. The demonstration by Heald *et al* [1] of mesorectal metastases distal to the site of the cancer has led many surgeons (including the authors of this paper) to perform total mesorectal excision for all rectal cancers, this inevitably involves either low colorectal or coloanal anastomosis[2]. The authors' statement that they performed mesorectal excision after the manner of Heald is not compatible with a 2.1 ratio of low.high anastomoses. Perhaps they included rectosigmoid junctional cancers in this series, in which situation total mesorectal excision is not advised[1].

Whatever the explanation, it behoves authors to be accurate in their use of precise surgical terms, otherwise the resulting confused literature will prevent meaningful or accurate reference in the future.

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Letter 2

Sir

I read with interest the article by Messrs Mealy, Burke and Hyland (*Br J Surg* 1992, **79**: 305–7) and would like to make the following points.

First, the authors are to be commended for a leakage rate of 5·3 per cent in their series of 114 consecutive anterior resections. However, I would suggest that, after a resection deep in the pelvis, fixation of the left colon by a stoma puts an unwarranted amount of tension on the anastomosis by fixing the colon to the anterior abdominal wall. Should it be felt necessary to defunction the anastomosis, surely a loop ileostomy is likely to result in less tension.

A further point is that all the patients who had a clinical leak underwent conversion to an end colostomy in the left iliac fossa which, as far as the patient is concerned, is the same functional outcome as abdominoperineal excision, i.e. a permanent end colostomy

I think that their abdominoperineal resection rate of 14·7 per cent is artificially low since the number of patients who received a permanent end colostomy in the left iliac fossa is clearly higher than the percentage rate they quote.

The other point that I feel needs to be made is that all the patients in whom clinical anastomotic dehiscence occurred required a further operation. By defunctioning an anastomosis with a loop ileostomy, even if clinical evidence of a leak occurs, most patients can be managed conservatively and subsequently undergo ileostomy closure when the anastomosis has healed. This reduces the chance of a permanent end stoma in the left iliac fossa.

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Letter 3

Sir

We read with interest the paper by Mr Mealy and colleagues (*Br J Surg* 1992, **79**· 305–7) on the safety of performing anterior resection without a defunctioning colostomy They make several points that we wish to address

The authors state that 'anterior resection was performed by standard methods with wide excision of the mesorectum' and quote the seminal publication of Heald *et al.*[1]. In fact the policy at Basingstoke is to perform *total* mesorectal excision, leaving behind a denuded stump of anorectum on to which the prepared colon is stapled It is our belief that mesorectal residues left clinging to the pelvis or levators after wide local excision form the basis of local recurrence. This is confirmed by the low rate of local recurrence of 3·7 per cent in the Basingstoke series

The series described by Mealy *et al.* has an abdominoperineal resection (APR) rate of 14·7 per cent; 114 anterior resections were included. In their discussion they state that they are unsure whether the Basingstoke series[2] included consecutive patients In fact it is clearly stated in the quoted paper that the series included 200 consecutive cases of stapled low anterior resection. The APR rate of 9·8 per cent also refers to a consecutive series of patients referred to Basingstoke District Hospital with rectal cancer This is an important point as our results would be worthless if cases were deleted from the series on an *ad hoc* basis

The substantially lower APR rate in our series would suggest that a larger proportion of low tumours are treated by low anterior resection with total mesorectal excision. In our series, as in that of Mealy *et al.*, the low stapled anastomosis is most at risk of leakage. The fact that most of the anterior resections carried out at Basingstoke have a low stapled anastomosis might account for the higher total leak rate seen in this series.

In our quoted paper[2] we did not state the clinically significant leak rate as our report concentrated on patients developing insidious peritonitis and fatal septicaemia. A recent analysis of our computer database shows that there have been 18 clinically significant leaks in 210 consecutive patients undergoing stapled anterior resection with total mesorectal excision, i.e. a clinical leak rate of 8 6 per cent Thirty-two patients had clinical or radiological leakage and the total leak rate was 15·2 per cent. In their series of 114 patients, Mealy *et al* have shown that 54 patients had a stapled anastomosis and six of these patients (i.e. 11 per cent) had a clinically significant leak Eight patients had clinical or radiological leakage, and the total leak rate is therefore 15 per cent in the stapled group. Thus the leak rates are in fact similar when comparing stapled anastomoses after anterior resection.

Our results[2] included 200 stapled anterior resections, of which 125 were defunctioned and 75 not. In the defunctioned group, one patient developed peritonitis following colonic necrosis but survived this complication. In the non-defunctioned group, six patients developed peritonitis ($P < 0{\cdot}01$) and three died. In the series of Mealy *et al*, among the subgroup of 54 non-defunctioned anterior resections with stapled anastomoses all six patients who suffered a clinical leak needed a further laparotomy with conversion to an end colostomy. Although they report the radiological leak rate in the defunctioned group of our series and the fact that peritoneal soiling and peritonitis can occasionally occur in patients undergoing defunction, they have not made any comment on the fact that defunctioning the low stapled anastomosis in our series was associated with a significantly lower incidence of generalized faecal peritonitis following leakage and a lower mortality rate. There has been no death in our series from closure of a defunctioning stoma Perhaps defunctioning their own low stapled anastomoses might have reduced the incidence of generalized peritonitis, the incidence of relaparotomy, and possibly prevented the one death.

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1. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? *Br J Surg* 1982; **69**: 613–16
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Authors' reply

Sir

We appreciate the interest shown in our paper by Messrs Meyrick Thomas, Cunliffe, Karanjia and Heald. We share Mr Meyrick Thomas's concern regarding the terminology of what is low or high in anterior resection He is right to infer that total mesorectal clearance was carried out in our patients as described by Heald *et al*. We do not understand his concern regarding the 74·40 ratio of low:high anastomosis, as these ratios are similar to those in other reports. Total mesorectal clearance does not necessarily mean a coloanal anastomosis as reflected in Heald's own data, in which at least 16 per cent of anastomoses are >6 cm from the anal verge[1] Others using this technique have reported up to 50 per cent of tumours >8 cm from the anal verge[2].

Confusion in this area remains because some series, as referred to above, report on either tumour or anastomotic height, these parameters themselves vary depending on digital or flexible or rigid sigmoidoscopic examination. Lack of uniformity in this area makes comparisons between series difficult For this reason our definition is derived from Turnbull *et al*[3], who defined high or low based on whether the anastomosis was above or below the peritoneal reflection, this overcomes any arbitrary division of the rectum and is anatomically objective We are presently examining tumour and anastomotic heights, degree of mobilization and clearance rates in an attempt to clarify this issue

Mr Cunliffe refers to our low abdominoperineal resection (APR) rate of 14·7 per cent. Even with the addition of the six permanent stomas following anastomotic dehiscence this gives an overall permanent stoma rate of 18·9 per cent, which is comparable to results of others[2] Furthermore, this assumes a 100 per cent closure rate for those who do advocate a defunctioning colostomy in addition to the permanent colostomies resulting from leaks in these series.

We disagree that a defunctioning stoma, either colostomy or ileostomy, will allow the conservative management of a significant anastomotic dehiscence. Anastomotic dehiscence, sepsis and resultant death have been reported in patients with defunctioning stomas after colorectal anastomosis[1]. Furthermore, the value of a defunctioning ileostomy in itself might be disputed because of the significant morbidity, reported by us[4] and others[5], in the closure of defunctioning ileostomies associated with restorative proctocolectomy. There is no reason to believe that ileostomy closure after anterior resection would have any lesser morbidity.

Messrs Karanjia and Heald comment on our term 'wide excision of the mesorectum' Although the terminology may be different, this does, we believe, correspond to their 'total mesorectal excision'.

The discussion of whether the Basingstoke anterior resection and the APR patients constitute a consecutive series refers to the fact that the quoted paper does not contain information from both groups, so it is unclear whether these consecutive series are contemporary

We found it interesting that the clinical leak rate was not reported in the Basingstoke series despite the obvious association between anastomotic dehiscence, peritonitis and septicaemia The similar leak rate between the two series again strengthens our contention that a defunctioning colostomy may be unnecessary at anterior resection.

The final point raised by Karanjia and Heald relates to the relative risks of not defunctioning the low anastomosis and the resultant potential complications against the relative risks of colostomy formation and closure. While there was no death from closure of colostomy in their series this is not always the case[6]; furthermore they neglect to highlight the very significant morbidity associated with this procedure demonstrated in their own results[1].

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Assessment of quality of life in surgery

Sir

We read with interest the review by O'Boyle (*Br J Surg* 1992, **79**· 395–8) on assessment of quality of life in surgery, particularly in the light of the recent publication of the National Confidential Enquiry into Perioperative Deaths (NCEPOD)[1] for 1990.

The methods of assessing quality of life are clearly useful in patients undergoing elective surgery, especially major procedures They do not, however, seem applicable to old infirm patients presenting with emergency and/or malignant conditions requiring major surgery Successful surgery and recovery may well allow such patients to return to their previous quality of life but failure may be attended by the death of the patient

The NCEPOD assessors criticised overaggressive surgical management in some of these patients Clearly individual patients need individual assessment, but we feel adequate attention was not given to consideration of potential quality-of-life benefits In our experience patients are often willing to accept a high operative risk if this potential exists. A prerequisite for such decisions is, of course, full and frank discussion

Studies such as NCEPOD, while laudable, cannot assess the potential quality-of-life gains of an individual patient. Furthermore, they do not take full account of patients undergoing similar procedures with the same risks who achieved the potential gains envisaged before the operation

We feel it would be wrong for patients to be denied the option of surgery when there are great potential gains in quality of life, albeit at the expense of a high operative risk.

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1. Campling EA, Devlin HB, Hoile RW, Lunn JN *Report of the National Confidential Enquiry into Perioperative Deaths 1990* London· The National Confidential Enquiry into Perioperative Deaths, 1992.

Author's reply

Sir

I agree with the comments of Sandison *et al* regarding the need to assess potential quality-of-life benefits for the individual patients undergoing high-risk surgery. They feel that quality-of-life measures may not be applicable to old infirm patients presenting with emergency and/or malignant conditions requiring major surgery in which failure may be attended by death of the patient It has been argued by others that quality-of-life assessments are generally not required when an intervention is very likely to save a patient's life and restore the patient promptly to his or her premorbid state of 'normal living'. There are, however, life-saving treatments that many reasonable people would reject because they would find the quality of life during or following their administration unacceptable. Such decisions will vary from individual to individual and there is obviously a need to make individually based judgements. Despite the difficulties, I believe that valuable information can be obtained from the application of quality-of-life measures, particularly those which are individually based, in patients undergoing such surgery.

Two factors require particular attention First, we need to know the degree of concordance between an individual's judgement of his or her quality of life and that of some external assessor, be it a surgeon or carer Second, it is clear that the frame of reference used by a person to evaluate their quality of life will itself be influenced by circumstances A patient may see things quite differently following a major intervention Aspects of life previously assigned little weight may assume increased importance after life-saving surgery In this context, we are presently assessing the postoperative quality of life of patients presenting with ruptured aortic aneurysms

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Audit of general practitioner referrals to an acute surgical unit

Sir

The recent paper by Dookeran *et al.* (*Br J Surg* 1992, **79**. 430–1) demonstrates not that general practitioners are falling down on their duties, but that inefficient organization of National Health Service resources results in an inefficient consumption of resources The consultation level was selected to be the least experienced and therefore presumably the least able to provide detailed advice To compound this, the person who assessed the arriving patients was also the least experienced member of the team, so it is hardly surprising that this resulted in inappropriate admission to hospital and undue consumption of resources. As the authors conclude, a great deal more efficiency could have been obtained had the general practitioner been able to speak to a surgeon with more surgical experience than himself, rather than less In addition, there can be no doubt that clinical examination of a patient by an experienced surgeon is by far the most important method of assessment in patients referred to acute surgical units I am surprised that the authors found it necessary to recourse to an audit of their activities to prove this

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Authors' reply

Sir

The practice of preregistration house officers accepting and arranging admission for acute surgical referrals from general practitioners is common in Leicester and in other hospitals in the Midlands (for example in Sheffield and Nottingham).

The outcome of our audit of general practitioner referrals to an acute surgical unit is particularly useful because it demonstrates that inefficiencies exist in the acute surgical service and quantifies the cost of these inefficiencies In this study the resultant cost was high – approximately £25000 We believe that audit is an excellent method of determining the cost-effectiveness and utilization of acute surgical facilities, and would encourage all surgeons to use audit as a method of improving the efficiency of their acute service.

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Attitudes of cardiothoracic surgeons in the UK to human immunodeficiency virus

Sir

We read with interest the paper by Roxburgh *et al* (*Br J Surg* 1992, **79**. 415–18) concerning the attitudes of cardiothoracic surgeons in the UK to the human immunodeficiency virus type 1 (HIV-1). We agree with their conclusions that HIV-1 testing and the refusal of surgeons to operate on such patients are not the answers to this problem We also agree that changes in operative practice and the institution of additional precautions are needed if the risk of infection to health workers is to be minimized. The authors concluded, however, that these changes will take time and require considerable resources

The maintenance of an intact barrier between the hands of the surgical team and the tissues of a patient is an important factor in preventing the transmission of disease. The effectiveness of surgical gloves in providing this mechanical barrier has been questioned[1,2] As Roxburgh *et al.* point out, glove perforation may occur in up to 20 per cent of surgical procedures[3], thus increasing the risk of cross-infection. Double gloving reduces the risk of cutaneous exposure to blood and body fluids[4] by 60 per cent, but the associated loss of tactile sensitivity may make surgeons (particularly vascular ones) reluctant to adopt this method of protection

In a study carried out in our department, nearly 70 per cent of all glove perforations detected during open heart surgery were shown to occur during sternotomy closure[5]. A subsequent prospective randomized trial showed that this incidence could be significantly reduced by the simple measures of either double gloving or wearing cotton gloves over a single pair of latex ones[6] In open heart surgery we have therefore identified a specific stage of the operation (sternal closure) during which the potential for glove perforation is greatly increased, and have also shown that simple additional protective measures reduce this risk As with all forms of additional protection, manual dexterity and comfort are reduced, but fortunately the stage of the operation at which the operating team is at most risk is also the stage requiring the least tactile sensation We would suggest that more widespread use of these simple precautions during sternal closure in cardiac surgery would enhance the safety of operation for both the patient and surgical team, and that these methods would not, as the authors suggest, be time consuming or expensive to implement

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Book reviews

Advice for House Surgeons

C. D Johnson. 210 × 140 mm Pp 52 Not illustrated 1992. Beaconsfield, UK Beaconsfield Publishers. £4 50

This is a slim volume designed to fit in the house officer's pocket. It is easily read, clear and concise, and full of essential, practical advice unclouded by theory. It attempts to cover the problems and procedures commonly encountered by junior doctors and, for the most part, provides simple, clear instructions. However, the depth of advice is somewhat variable For example, there are precise details of heparin treatment, pain relief and fluid management, but premedication is sketched over and warfarin therapy and the management of the diabetic patient after operation not mentioned at all. The problem with writing such a book is to steer a path between one's own approach to a situation and that adopted by other people. The author avoids appearing too didactic, making ample allowance for local variation in custom, but in doing so sometimes fails to provide sufficient advice. In addition to practical guidance, this volume is an essay on communication, impressing on the reader the importance of liaison with other hospital and outside staff, from the porter to the radiographer and the staff nurse to the coroner's officer. In summary, this is an excellent book that provides a mass of useful advice on all sorts of situations important to the house surgeon. The information is packed into a small easily read volume that should be readily assimilated by the apprehensive fledgling house officer

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Atlas of Cutaneous Laser Surgery

D B Apfelberg (ed) 281 × 222 mm Pp. 483. Illustrated New York Raven Press 1992 US $244

This well illustrated book is truly an atlas of cutaneous laser surgery There are multiple authors; the text is divided into one chapter on physical principles of lasers, two on laser safety, and thereafter takes case-report form covering patients treated with carbon dioxide (CO_2), argon, yttrium–aluminium–garnet, tunable-dye and, lastly, newer laser technologies. Each case occupies around two pages, with multiple pictures of before-and-after results accompanied by a fairly brief text. The section on the CO_2 laser is largest and, while it includes many conditions that one would accept are well treated by this laser, such as rhinophyma and actinic cheilitis, there are others which are rather surprising, such as pyogenic granulomas and onychomycosis. I was impressed by the results, shown photographically, of treating scarring of chronic discoid lupus by CO_2 laser and also by the cosmetic improvement in a patient with extensive neurofibromatosis, but, overall, I did feel that some of the indications for laser therapy were slight. In the argon laser section – as one would expect – angiomatous lesions predominate, and there was a tendency to treat those that dermatologists would observe in the justified belief that natural regression will take place However, both angiofibromas and tuberous sclerosis were impressively treated in this section

In the section on tunable-dye therapy, telangiectasis, cherry angiomas and spider angiomas are discussed; it would have been useful to have had a comparison with results using the infra-red coagulator. Overall this is a well illustrated book, but I felt it would have been more valuable with clear indications as to what to treat and when, and thereafter some discussion on the reasons for choosing the particular laser selected for therapy. The book tends to leave one with the overall impression that those who have access to a laser are naturally enthusiastic to maximize its use without, perhaps, critically assessing the value of this therapy compared with other available methods In general, the colour pictures are of high quality and those interested in laser therapy will see a wide range of approaches

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Case Presentations in Arterial Disease

D. Bouchier-Hayes, P. J Broe, P. A. Grace and D Mehigan. 210 × 130 mm. Pp. 139 Not illustrated 1991. Oxford Butterworth–Heinemann. £14·95

This little book gives 69 case histories of patients with vascular disease No attempt is made to provide feedback to the reader on how well or badly they have diagnosed and assessed each case, although each history is followed by a comment where the diagnosis is discussed and a 'discussion' that expands on the original topic. This is the method by which most of us learn our medicine, although a text rather than a patient means that the clinical examination cannot be assessed and is simply provided. Unfortunately, clinical examination skills are often the most difficult part of a student's education. I personally do not like this type of exercise and would not encourage students to go out and buy this book, although I recognize that there are many students who do find this type of presentation attractive and for them the book may prove useful It is a pity that the volume is broken up into different sections as this makes it considerably easier to guess at the diagnosis It is extremely doubtful whether many students need such a specialized text as they are hard-pressed to read even small surgical textbooks in 1992.

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Principles of Cardiac Diagnosis and Treatment – A Surgeon's Guide. 2nd ed.

D Ross, T English and R McKay 243 × 169 mm Pp 269 Illustrated. 1992 London Springer-Verlag £49 50.

The second edition of this book, which is already well established as a 'surgeon's guide', has been thoroughly revised and updated by a triumvirate of distinguished cardiac surgeons The text is directed towards residents and trainees in cardiothoracic surgery but will find a ready audience among nurses, radiologists and physiotherapists who are engaged in this branch of surgical management.

The book is of convenient size and weight; it is produced in clear type and beautifully and copiously illustrated by Barbara Hyams with 169 clear line drawings There are many additional carefully selected photographs and radiographs.

The entire text is relevant and represents the basic knowledge required by those who are learning to work effectively in this complex field. The surgeon who is ultimately responsible for the patient's safe passage during and after operation must be confident of the exact diagnosis of the patient's condition and familiar with the 'tools of diagnosis' that are now available to the cardiologist before the patient is selected for surgery Modern developments and special investigations are outlined in the context of the way this subject has developed historically Brief descriptions of echocardiographic techniques, radionuclide studies, computed tomography and magnetic resonance imaging are included. These complement Donald Ross's excellent essay on the 'Clinical aspects of cardiac diagnosis', which is reproduced from the first edition. A new section of ten pages describes methods that are now available for circulatory and respiratory support. A large section of 100 pages is devoted to a detailed description of congenital heart defects and, although no mention of its incidence was found, this is comprehensive and based on the nomenclature and sequential analysis of cardiac anatomy. A shorter section of 48 pages is devoted to acquired valvular, coronary artery and miscellaneous heart disease.

This updated edition is beautifully written and presented It is essential reading for all who wish a sound grounding in the principles of modern cardiac surgery and patient management.

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Urological Oncology – Reconstructive Surgery, Organ Conservation, and Restoration of Function

P H Smith and M Pavone-Macaluso (eds) 235 × 155 mm Pp 418 Illustrated 1991. New York Wiley–Liss US $99 95

This book (Volume 370 in the *Progress in Clinical and Biological Research* series) is a compilation of the contributions to the Sixth Course in Urological Oncology held in Sicily in March 1990 and provides the tenth such monograph of the Genitourinary Group of the European Organization for the Research and Treatment of Cancer. The theme of this particular course was the principles of preservation and reconstruction in the management of patients with urinary tract malignancy. The outstanding advantage of this type of book is that it gives the reader the opportunity of availing themselves of an up-to-date review of the techniques and results of internationally renowned units famous for particular innovative approaches to treatment

Some contributions are relatively brief but others are 'state of the art' reviews that would justify leading article status All the papers are well referenced and provide the reader with an excellent source of review material There are also stimulating and significant contributions in the research and development field that are very well presented by well known urologists with a major interest in oncology. The editors are to be congratulated on the high literary standard of the text because many of the contributors do not have English as their first language This excellent book has stimulated me to look at previous monographs in this series

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Surgery Annual 1992. Part 1

L M Nyhus, ed 235 × 155 mm. Pp 258 Illustrated 1992. Connecticut Appleton and Lange. US $103·50

The preface to this book states that it presents 'critical discussion of recent developments in the clinical management of surgical diseases, reports advances in the basic sciences as they relate to the practice of surgery, and discusses social and economic issues important to surgeons and patients' This is a wide-ranging brief and, in addition, the individual chapters are intended to be of interest to 'practitioners of many specialities' In this volume subjects include endovascular surgery, fractures of the distal radius, liver transplantation in children, and advances in neuroblastoma. Most chapters, however, deal with general surgical topics, 'An overview of surgery 1992' covers a range of topical subjects including breast screening, laparoscopic surgery, and acquired immune deficiency syndrome There are excellent chapters on the incidence, aetiology and treatment of peritoneal adhesions, and the management of severe intra-abdominal infection A chapter on percutaneous endoscopic techniques for the removal of gallstones is rather disappointing. The authors (both urologists) report a series of 16 laparoscopic cholecystectomies but, as some series now contain over 500 patients, this experience would hardly seem relevant

Text on pylorus preservation in duodenopancreatectomy, integrated ambulatory foregut monitoring, and surgical applications of the functions of the pylorus give something of an upper gastrointestinal bias to the volume Pylorus preservation is supported as producing superior gastrointestinal function, but a significant problem of anastomotic ulceration is conceded and only theoretical solutions to the problem advanced. Both 'Ambulatory foregut monitoring' and 'Surgical applications of the function of the pylorus' are of considerable theoretical interest, but the practical applications of these topics are perhaps overstated 'Endovascular surgery' includes descriptions of several commercially available atherectomy devices, which is surprising as the authors admit that this field is still experimental. 'Liver transplantation in children' describes the increasingly acceptable results that can be obtained with recent advances in this procedure.

Although individual chapters are of high quality and are well referenced, it is not easy to see where this book's appeal will lie Most chapters are aimed at general surgeons but others on liver transplantation in children, neuroblastoma, fractures of the distal radius and, perhaps, endovascular surgery will have little appeal to this readership. Similarly, paediatric, orthopaedic and vascular surgeons will not find this volume good value for money.

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General Surgical Oncology

G. Steele and B Cady (eds). 267 × 188 mm Pp. 366 Not illustrated 1992. Philadelphia W B. Saunders. £34.

I had difficulty in understanding the choice of title for this book since it seems to cover the oncological component of the management of patients presenting to clinicians practising in every branch of surgery. All the contributors work together in a purely tertiary referral environment in one institution in North America and have approached their task in idiosyncratic ways. Some sections represent an overview of the world literature – a 'recent advances' approach, some a non-peer reviewed overview of the author's own experience, and some an 'ego trip'. That this has been appreciated by the editors is exemplified by their statement in the preface that they 'themselves recognize that what has been written may not necessarily be a customary, let alone balanced, approach.'

I enjoyed the opening thought-provoking treatise on surgical research, the training needed for it, and the cogent arguments for clinicians to be involved in basic laboratory studies I envied the authors the environment which allows them to advocate that 'at least 45 minutes to an hour must be spent with the patient and family, sometimes on more than one occasion '. Unfortunately, few of the sections follow this initial philosophy and statements such as 'with experience however based upon visual inspection and palpation of the tumor one can usually decide initially if a limited resection will be feasible and adequate' are followed by 15 anecdotal case reports. There is some scientifically based iconoclasm, especially in the chapters on breast cancer and melanoma, although it is a pity the gynaecologist writing of the management of melanoma in his field appears not to have read the earlier chapter

At the end I am left with the question 'At whom is this book aimed?' Its production may have 'actually been fun' for the editors but I found it rather dry and didactic – but in my copy pages 147–78 were missing so I cannot comment truthfully on the book as a whole. A candidate approaching a higher professional examination in surgery in general might find it useful but the rest of us are less likely to profit from this expensive volume

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Year Book of Dermatologic Surgery 1992

N A Swanson, R G Glogau and S J. Salasche (eds). 237 × 157 mm Pp 250 Illustrated. 1992 St Louis, Missouri Mosby–Year Book. US $59·95

This volume forms the most recent addition to the Year Book series, which is produced in the USA The principal editor in his introduction justifies its production by the fact that there has been an expansion during the past decade in the specialty of dermatology It deals with the surgery, in the broadest sense, of the skin

The book is divided into four sections. The first, 'Concepts and techniques', deals with wound healing, basic surgical techniques, nail surgery, laser surgery and complications of the application of some of these The second considers 'Oncology' and provides a good overview of the current position of the management of skin malignancy The third section, 'Reconstruction', would not be out of place in a textbook of plastic surgery. There are numerous complex reconstructive procedures and techniques described that tax the trained plastic surgeon in their application, many of which cannot be recommended to the general surgeon let alone the dermatologist The fourth section covers 'Esthetic dermatologic surgery'. Here various methods of dealing with varicose veins are described along with the surgical management of male pattern baldness, liposuction, fat transplantation, face lifting and blepharoplasty. In short, a range of aesthetic operations is considered.

This publication is directed at 'dermatologic surgeons', a specialty that does not exist in the UK It does describe part of the scope of modern plastic surgery and may be of interest to trainees in that specialty. Many of the inclusions, however, describe complex techniques that cannot be recommended to the occasional operator

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Volume II – Cancer Surveys. Prostate Cancer – Cell and Molecular Mechanism in Diagnosis and Treatment

J T Isaacs 261 × 183 mm. Pp 287. Illustrated 1991 USA Cold Spring Harbor Laboratory Press.

Cancer of the prostate is the current topic in the field of urology that attracts the most attention. This book is a timely addition to the literature and will go a long way to enhancing knowledge of this disease. The first section (Chapters 2–7) discusses the role of various genetic changes in prostatic carcinogenesis. It reviews what is already known and describes new experimental approaches relating to the unknown fundamentals of prostatic carcinogenesis and progression. The second section (Chapters 8–12) focuses on the role of cellular growth factors in the evolution of the disease. The third (Chapters 13–18) overviews the present status of endocrine therapy, the achievements and limitations, and presents new approaches to the therapeutic management of androgen-independent prostatic cancer. Each chapter addresses a particular area, clarifies the present state of knowledge and provides vision of possible future goals. I found the references valuable. This is a book that is extremely worth while for all interested in this disease, clinicians and researchers alike.

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Hydatid Disease – Current Medical and Surgical Management

D L. Morris and K S Richards 246 × 159 mm. Pp 150 Illustrated 1992 Oxford. Butterworth–Heinemann. £35

Professor Harold Dew of Sydney produced his landmark text on hydatid disease as long ago as 1928. Strangely, neither in the British Commonwealth nor in North America has there been any further surgical text on the subject. Two very useful publications have, however, emanated from Iran[1] and Libya[2]. This monograph consisting of 125 pages makes no claim to be an exhaustive dissertation on hydatid disease, but is an excellent source of information for surgeons and trainees. The reading task is not onerous, for 42 pages are taken up by illustrations.

The first chapter deals very adequately with the biology of *Echinococcus granulosus* and there is good discussion of the clinical value of serology. In the diagnostic section an important plea is made to the interventional radiologist to avoid percutaneous aspiration. Discussion of the surgical treatment is confined largely to hepatic cysts. It follows conventional surgical practice in Australasia, notably in advising cystectomy with deroofing of the cyst followed by omental packing and drainage. There follows an excellent review of the recent laboratory and field studies in chemotherapy. The current clinical position of mebendazole and albendazole is stated clearly and guidelines for their use established. Finally, alveolar hydatid disease caused by *E. multilocularis* is reviewed. This book is highly recommended.

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1 Saidi F *Surgery of Hydatid Disease*. London. WB Saunders, 1976.
2. El Mufti M. *Surgical Management of Hydatid Disease* London. Butterworths, 1989.

1001 Multiple Choice Questions and Answers in Surgery

A J Harding Rains. 216 × 138 mm Pp 189 Not illustrated 1992 London Chapman and Hall £10 95

This is the third edition of *Multiple Choice Questions and Answers in Surgery* based on that hardy perennial *Bailey and Love's Short Practice of Surgery* (now in its 21st edition). The questions have been compiled by Harding Rains, the Consulting Editor for *Bailey and Love*. The book opens with a brief introduction on multiple choice questions and methods of tackling them.

The multiple questions are in the widely used format of a stem statement followed by five possible completions. The 1001 questions are divided into three sections, the first is the easiest in that there is only one correct answer of five for each question. The second and third sections are more difficult as any or all the answers may be correct. In the first and second sections the questions are arranged in the order of the chapters in *Bailey and Love* as an aid to revision, in the third section they are in a random order to simulate the exam situation.

Overall I think this a well produced book that I would unreservedly recommend to junior surgical trainees and medical students who use *Bailey and Love* as their surgical textbook. As the questions in the first two sections are in the order of the *Bailey and Love* chapters, it is possible to test one's knowledge as one progresses. However, the lack of an index or even subject headings throughout the first two sections to indicate the subject covered by a particular group of questions limits the value of this book as a revision aid for those not using *Bailey and Love*.

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A Very Short Textbook of Surgery. 2nd ed.

P Ryan 211 × 149 mm Pp 87 Not illustrated 1990. Melbourne, Australia Dennis and Ryan

This extremely compact book is aimed at the junior medical student and summarizes the principal differential diagnoses of commonly presenting symptoms in surgery, together with rather variable detail on investigation and management. Each chapter is clearly presented but assumes that the student will refer to a larger textbook for definitions and descriptions of the many terms used. Most conditions are included, although acute ischaemia does not feature in the differential diagnosis of upper limb pain. Moreover, in its attempt to maintain brevity, there is little to guide the student to discriminate between important diagnoses. Thus one might have expected a little more than just resorting to an 'immediate technetium scan' to differentiate between testicular torsion and acute epididymitis, while omitting any reference to the importance of considering the patient's age or even whether he has had a recent urinary tract infection. As with any single-author text, the content and emphasis inevitably reflect personal opinion and experience; some advice remains controversial, most notably the statement that one should perform below-knee amputation if gangrene affects more than one toe or all of the great toe. While this book will appeal because of its brevity and principal aim of concentrating on symptoms, it may well be superseded by the more recent slightly larger pocket-size publications which provide more in the way of clinical detail, space to write notes, and integrated rationales of investigation and management.

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Notices and announcements

8–10 November 1992
Society for Minimally Invasive Therapy Fourth Annual World Conference
Dublin, Ireland
Information Mr N N Williams, Department of Surgery, Mater Hospital, 47 Eccles Street, Dublin 7, Ireland

9–13 November 1992
Annual Course in Hepatobiliary and Pancreatic (HPB) Surgery
London, UK
Information Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

13 November 1992
Symposium on Liver Transplantation
London, UK
Information. Mr N A. Habib, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

15–18 November 1992
Update and Future Trends in Fibrin Sealing in Surgical and Non-surgical Fields
Vienna, Austria
Information Univ Prof. G Schlag, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstraße 13, A-1200 Vienna, Austria

15–21 November 1992
Advances in Cancer Treatment
London, UK
Information. Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

16–20 November 1992
Research Methods in Surgery
London, UK
Information· Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

16–21 November 1992
XXVIII World Congress of the International College of Surgeons
Cairo, Egypt
Information. EMECO Travel, 2 Talaat Harb Street, PO Box 1294, Cairo, Egypt

25–28 November 1992
Recent Advances in Anaesthesia, Pain, Intensive Care and Emergency
Trieste, Italy
Information Trieste Traduzioni Congressi, Via C. Battisti 1, 34125 Trieste, Italy

3–5 December 1992
Special International Columbus Meeting on Surgical Oncology
Genoa, Italy
Information Italiana Congressi, Via P E. Bensa 2/6A, 16124 Genoa, Italy

4–5 December 1992
8th International Steglitz Paediatric Surgical Congress: Endoscopic Surgery in Children
Berlin, Germany
Information Dr F. Schier, Kinderchirurgie, Universitätsklinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany

8–10 December 1992
Seventh International Workshop on Therapeutic Endoscopy
Hong Kong
Information· Dr S. Chung, Combined Endoscopy Unit, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

10–11 December 1992
Reconstruction in Surgical Oncology
Genoa, Italy
Information Anna Guida, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10-16132 Genoa, Italy

11 December 1992
Role of the Plain Abdominal Radiograph in the Acute Abdomen
Canterbury, UK
Information Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

3–6 January 1993
Postgraduate Course in Gastroenterology
Oxford, UK
Information Dr D. P. Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

7–8 January 1993
Surgical Research Society Meeting
London, UK
Information Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

16–17 January 1993
Hong Kong Surgical Forum – Winter 1993
Hong Kong
Information Alice Iu, Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

5 February 1993
Transjugular Intrahepatic Portocaval Shunts
Toulouse, France
Information Service d'Hépato-Gastro-Entérologie, CHU Purpan, 31059 Toulouse, France

8–10 February 1993
Child Safety in Southern Africa
Cape Town, South Africa
Information· Deborah McTeer, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape, South Africa

18–20 February 1993
Colorectal Disease in 1993: an International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information. The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Room TT-31, Cleveland, Ohio 44195-5241, USA

21 February 1993
Phlebology Review
Lake Buena Vista, Florida, USA
Information· North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, California 92024, USA

22–24 February 1993
Sixth Annual Congress of the North American Society of Phlebology on the Advances in Sclerotherapy and the Advances in Surgical and Medical Treatment of Venous Disease
Lake Buena Vista, Florida, USA
Information. North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, California 92024, USA

12–15 March 1993
7th Congress of the Western Pacific Association of Critical Care Medicine
Hong Kong
Information. Ms E. Lindsay, Secretariat, International Conference Consultants Ltd, Suite A/B, 16 F, Casey Building, 38 Lok Ku Road, Sheung Wan, Hong Kong

19–20 March 1993
2nd European Congress on Ambulatory Surgery
Brussels, Belgium
Information Dr Cl. De Lathouwer, Brussels One Day Clinic, Nouvelle Clinique de la Basilique, 37–47 Rue Pangaert, B-1080 Brussels, Belgium

31 March–2 April 1993
UICC Kyoto International Symposium on Recent Advances in Management of Digestive Cancers
Kyoto, Japan
Information. Professor T. Takahashi, Department of Surgery, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602, Japan

14–16 April 1993
Association of Surgeons of Great Britain and Ireland Annual Meeting
Birmingham, UK
Information. Caroline Ross, Association of Surgeons of Great Britain and Ireland, at The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

8–11 June 1993
World Association of HPB Surgery 1st European Congress of Surgery
Paris, France
Information· EHPBS Congress Secretariat, Congress House, 65 West Drive, Cheam, Surrey SM2 7NB, UK

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The North Pacific Surgical Association
The Society for Clinical Vascular Surgery
The Society of Head and Neck Surgeons
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For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991, **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

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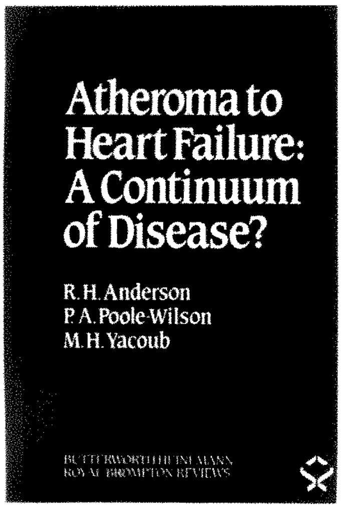

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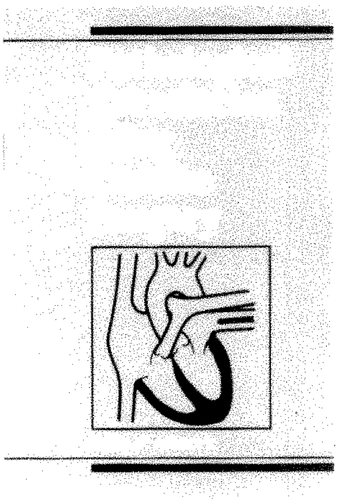

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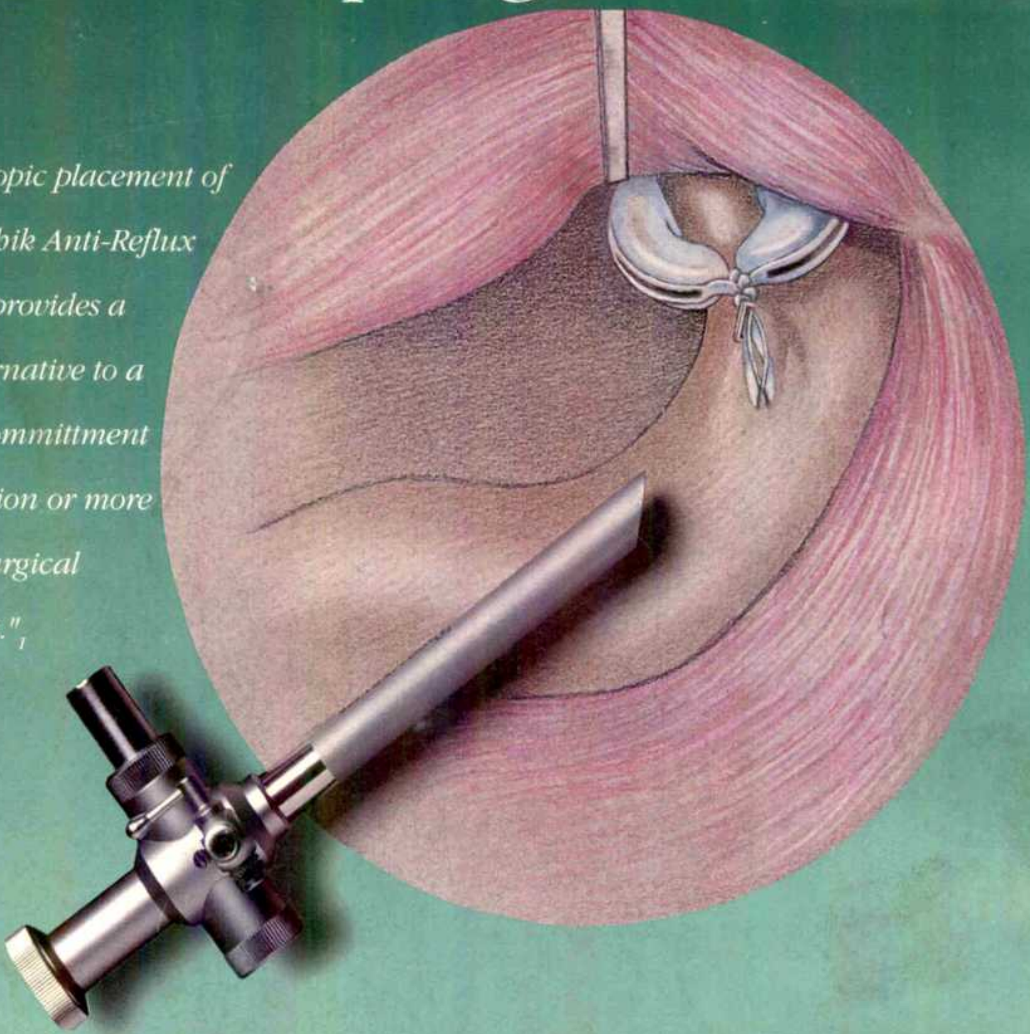

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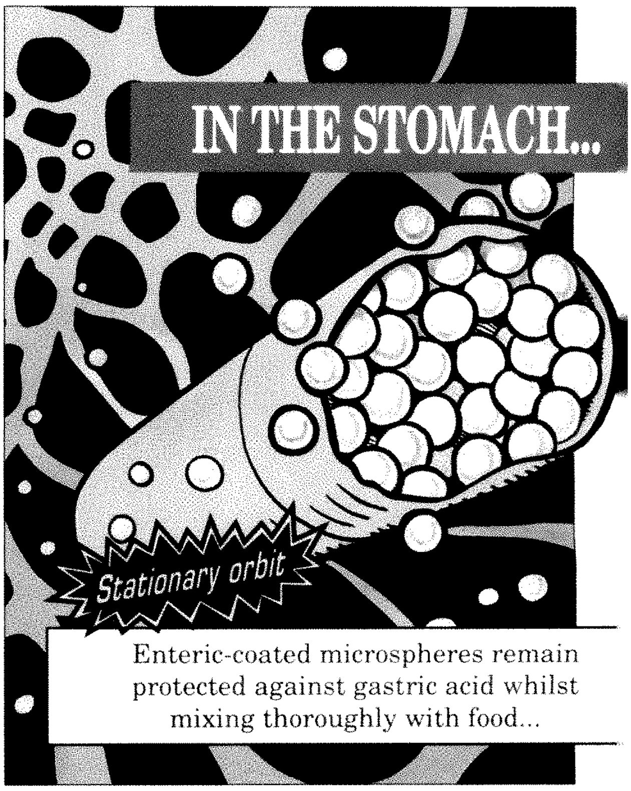

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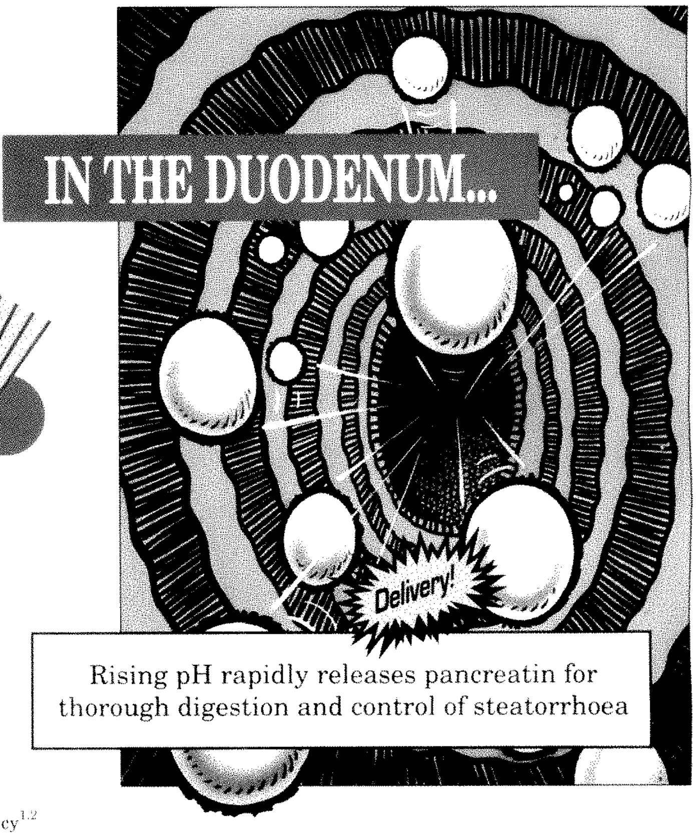
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1. Stead R J et al. *Thorax* 1987; **42**: 533-37
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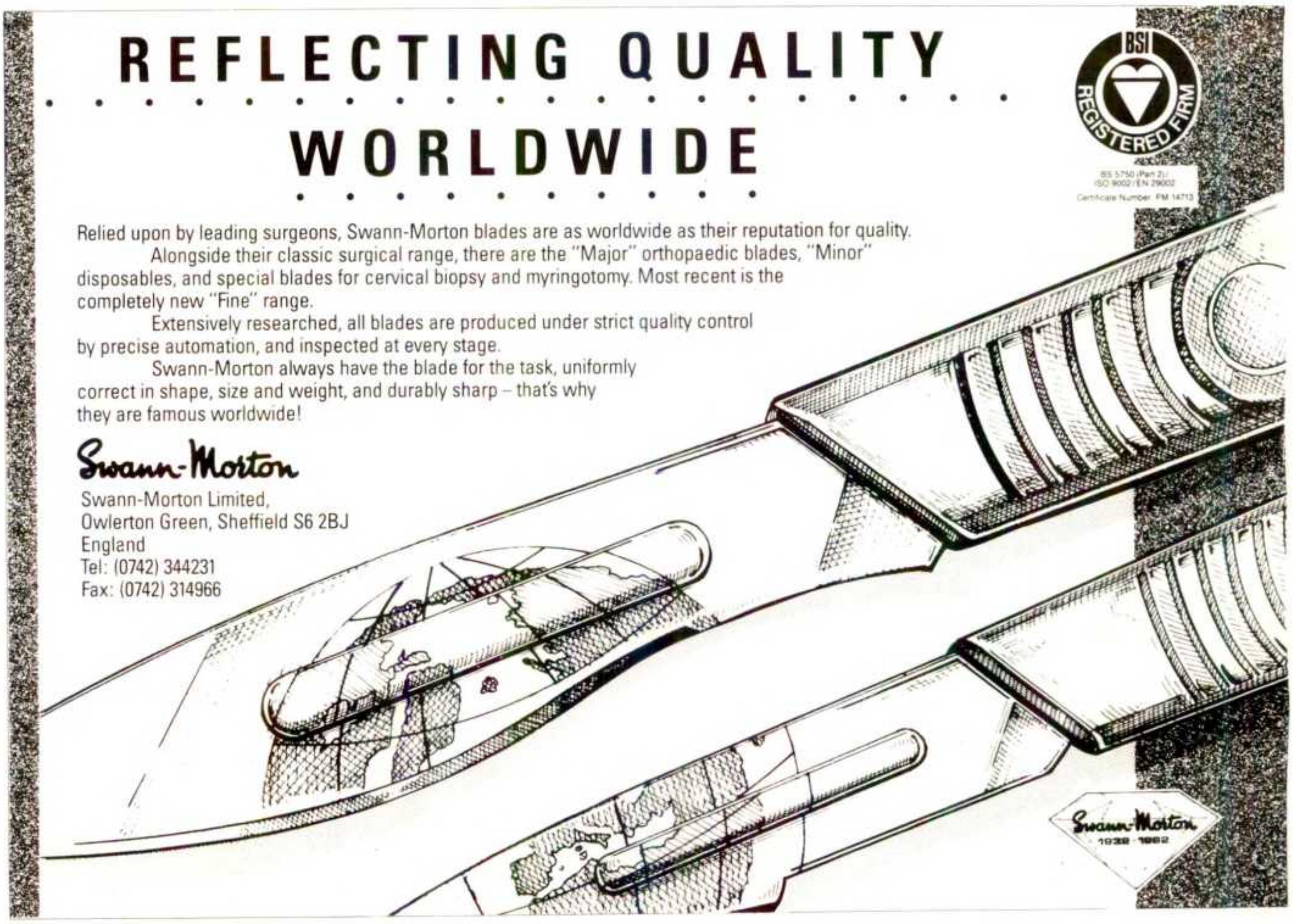

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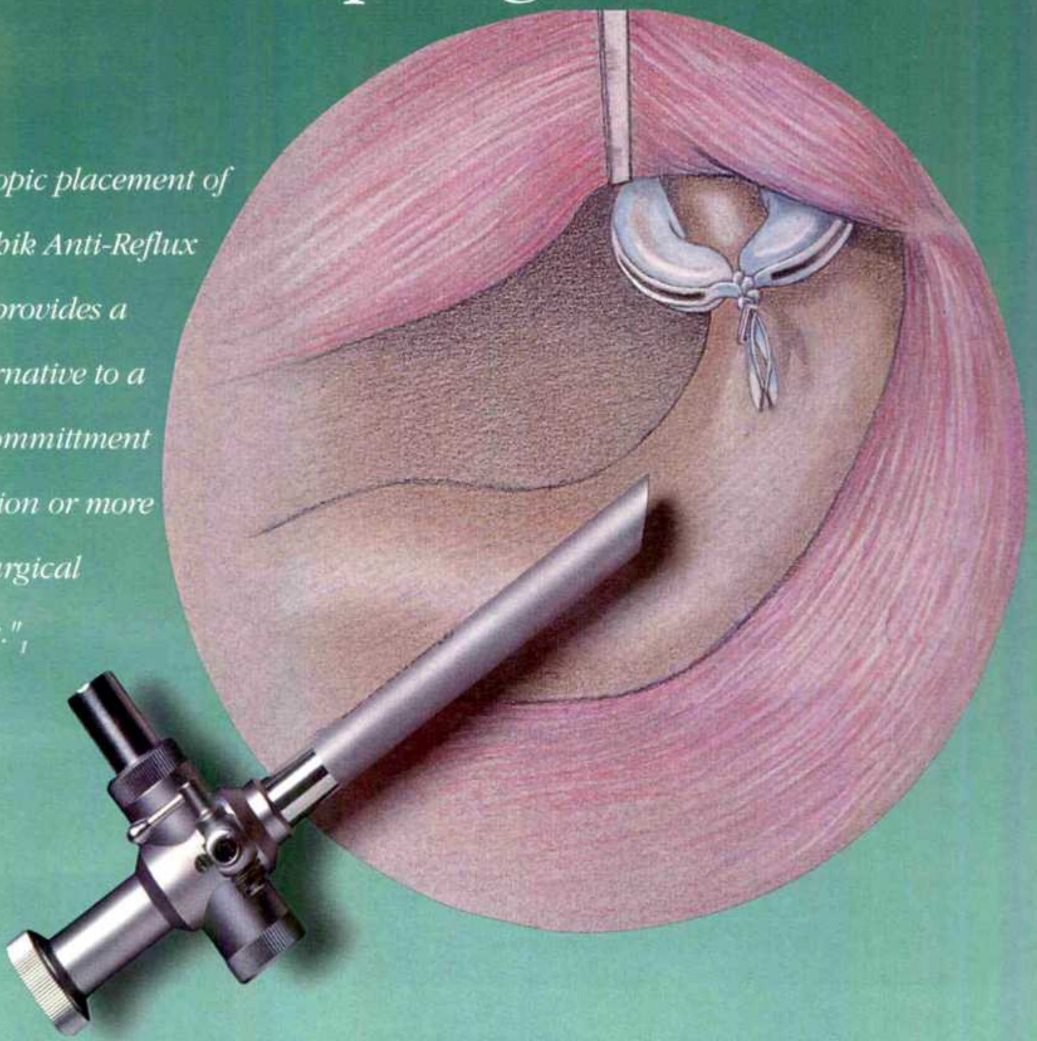

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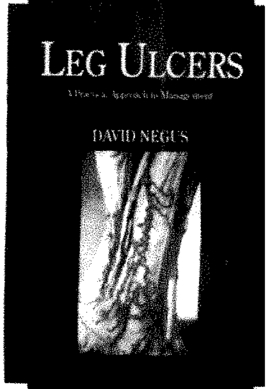

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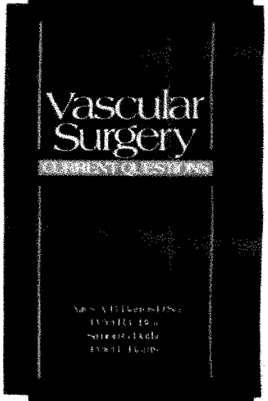

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Br. J. Surg. 1992, Vol. 79,
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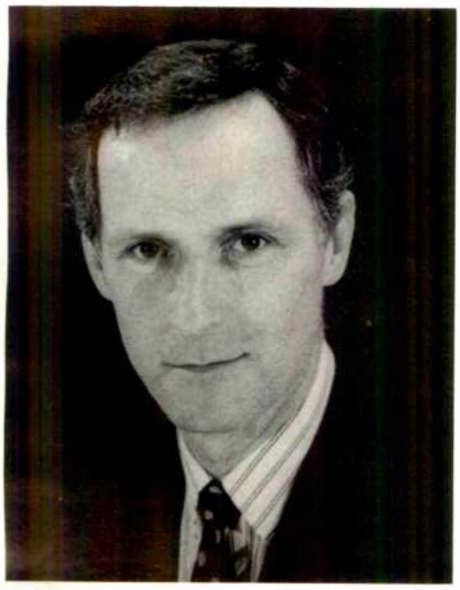

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Samuel Thomas Donnan McKelvey (born 1935) is a consultant surgeon at the Ulster Hospital, Dundonald, Belfast. His basic medical education and surgical training were undertaken in Northern Ireland except for 3 years at Newcastle upon Tyne. He became a consultant senior lecturer at The Queen's University Belfast in 1974, before taking up his present post in 1985. He is a surgical gastroenterologist with particular interests in peptic ulcer disease and colorectal carcinoma. His Hunterian Lecture (1987) concerned the influence of gastric and biliary surgery on the colon.

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Charles Nevin McCollum (born 1950) is Professor of Surgery in Manchester University at the University Hospital of South Manchester (since 1989). After qualifying from Birmingham University he worked in Nottingham, Leeds and Birmingham, moving to Charing Cross Hospital as a consultant senior lecturer in 1983. He is a vascular surgeon with academic interests in graft patency, ischaemia–reperfusion injury and platelet function. He is a previous winner of the Moynihan Prize, Patey Prize, Hahn Prize (European Society of Cardiovascular Surgery) and a Hunterian Professorship.

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Francis Brian Vincent Keane (born 1945) is a consultant surgeon to the Meath and Adelaide Hospitals, Dublin, and a senior lecturer at Trinity College, Dublin. His surgical training in England and Ireland was punctuated by 18 months as a research fellow at the Mayo Clinic in Minnesota, USA. He is an examiner for the FRCS Ireland. His clinical interests are in upper gastrointestinal and HPB surgery with recent concentration on lithotripsy and laparoscopic surgery for gallstones.

MR DAVID LEAPER

David John Leaper (born 1947) is a consultant senior lecturer at Southmead Hospital, Bristol. He graduated from Leeds and after junior appointments in Yorkshire (Leeds and Scarborough) gravitated to London (King's and Westminster) before joining the Department of Surgery in Bristol. Distinctions include an SRS European Fellowship and Hunterian Professorship. He is Editor of *Surgical Research Communications* and a member of the Court of Examiners of The Royal College of Surgeons of England. His particular interests are in breast disease, surgical infection and wound healing.

Robin Williamson

Br. J. Surg. 1992, Vol. 79, November, 1123–1124

Laparoscopic herniorrhaphy

'When you have a new hammer, every problem seems like a nail.'

Armed with the new 'hammer' of therapeutic laparoscopy, general surgeons have looked for appropriate 'nails' in the abdominal cavity. No organ or procedure appears immune. At the 1992 World Congress of Endoscopic Surgery, the evidence for this success was on display. Laparoscopic vagotomy, partial gastrectomy, splenectomy, small and large bowel resection, anterior resection and even adrenalectomy have now all been successfully performed, and many more beside. With the exception of bowel resection, these advances seem unlikely to impact on the day-to-day workload of the average surgeon, but what of inguinal hernia repair, very much the staple diet of the general surgeon? Given that virtually every surgical unit in the Western world now has laparoscopic equipment and skills, can laparoscopic surgery possibly offer any advantage over conventional repair, a technique that has been refined and improved since Bassini's original description in 1884 and which apparently enjoys a high success rate, and can usually be performed on a daycare or overnight stay basis?

The excellent results of conventional repair reported from specialist centres are well known. The Shouldice Clinic[1] has a remarkably low recurrence rate of 0·6 per cent for over 6000 hernia repairs with a minimum follow-up of 10 years. Even when this technique is exported from the specialist setting, the results are impressive; the combined experience of several surgeons using the Shouldice repair on over 22 000 hernias has resulted in a recurrence rate of 1·3 per cent[2]. Other reports, however, suggest that the results of repair in the surgical community at large are not so impressive; recurrence rates of between 16 and 35 per cent have been reported. Devlin[3] has drawn attention to the fact that many published series are defective both in length of follow-up and in numbers lost to follow-up, suggesting that true recurrence rates may be higher than those commonly reported in the literature.

Traditional inguinal hernia repair is not without other complications. The ilioinguinal, iliohypogastric and both the genital and femoral branches of the genitofemoral nerve are at risk. Division of one of these may result in an area of anaesthesia that generally resolves within 6 months, but nerve entrapment by a suture may result in prolonged discomfort, pain or dysaesthesia. The testicular blood supply may be impaired resulting in testicular atrophy, even after an apparently uneventful repair at which the surgeon was unaware of inflicting vascular damage. Swelling of the testis due to trauma to the venous or lymphatic vessels of the cord or to 'too tight' a repair are other recognized complications.

In an attempt to avoid some of these, primary inguinal hernia repair using prosthetic mesh was introduced; it was popularized, especially in France, by Rives[4] and Stoppa and colleagues[5]. Lichtenstein *et al.*[6] have advocated the 'tension-free' hernia repair. By inserting a prosthetic mesh extraperitoneally to create a new inguinal floor, with no attempt being made to approximate the hernial margins, it was believed that pain, the complications resulting from an overtight repair, and recurrence rates would all be reduced. The recently reported experience using this technique, involving over 3000 patients, has shown a recurrence rate of only 0·5 per cent[7].

Encouraged by this experience, laparoscopic surgeons have applied the principle using a transperitoneal approach to a tension-free repair. Initial techniques involved placing a prosthetic plug or roll of polypropylene mesh into the inguinal canal, followed in some cases by stapled transection of the reduced peritoneal sac[8,9]. The recurrence rate from such techniques proved unacceptably high and these methods have become discredited and abandoned. Suture techniques have included simple closure of the internal ring with or without reduction of the sac[10] and suture plication of the transversalis fascia and the iliopubic tract[11]. These have, however, not found favour, perhaps because laparoscopic suturing techniques are technically demanding and time consuming, but perhaps also because they do not observe the 'tension-free' principle. The results of these methods are not yet available.

A third laparoscopic technique involves laying a prosthetic mesh over the myopectineal orifice and securing it in place with staples[12]. While no results have been published, there are conceptual concerns about this technique. Besides the risks

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of bowel adhering to the mesh, the failure of the technique to ligate let alone excise the sac violates a basic principle of hernia repair. The preperitoneal approach to perform a mesh repair, described by McKernan, has been taken up by several workers. Although technically demanding, risks of pneumoperitoneum are avoided.

The most popular method of laparoscopic hernia repair currently practised involves elevation of the peritoneum from the myopectineal orifice with ligation or excision of the sac, followed by placement of a prosthetic mesh which is stapled into place around three sides of the myopectineal orifice (the iliac vessels inferiorly obviously cannot be stapled) before the peritoneum is closed over the mesh. In a recent review of 359 laparoscopic repairs performed in several centres in the USA, with a follow-up of 13–104 months, MacFayden[13] found a recurrence rate of 0·8 per cent. Most patients returned to full activity within 1 week. The technique was not, however, free of other complications, which included: testicular, cord and anterior thigh pain; osteitis pubis; haematoma of the scrotum, inguinal canal and anterior abdominal wall; scrotal hydrocele; and bladder injury. The overall incidence of complications was just under 10 per cent.

Clearly the new technique is not without its problems and must still be considered under development. The complications may well be reduced as experience is gained, but only after long-term follow-up will the true recurrence rate be known. The advantages, if any, of laparoscopic over conventional hernia repair at present remain unproven. In the case of transperitoneal repair, by violating the peritoneal cavity, it exposes the patient to the risk, albeit low, of visceral or major vessel injury. It also requires general anaesthesia. Surgeons should not rush to adopt laparoscopic hernia repair in the way that they have adopted laparoscopic cholecystectomy. Only randomized prospective trials will demonstrate whether the method represents an advantage in hernia repair that can confidently be recommended to patients.

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Br. J. Surg. 1992, Vol. 79, November, 1125–1126

Intraoperative balloon angioplasty

Percutaneous balloon angioplasty (PTA) was first described in the management of peripheral vascular disease by Dotter and Judkins[1] in 1964. The technique relies on the principle of using an intraluminal balloon to dilate an arterial stenosis or occlusion to such an extent that the arterial intima, media and any associated plaque split, in effect producing a new 'lumen'. Although this was crude in approach, early patency rates after treatment of short occlusions or stenoses compare favourably with those after surgical bypass in the iliac and femoral arteries. PTA may be particularly valuable in elderly patients who are not fit for aortoiliac surgery but require an improvement in inflow before femoropopliteal or distal bypass for limb salvage. Despite reported high rates of early technical success, there is a shortage of published controlled studies regarding the medium- and long-term clinical efficacy of PTA. Although most workers carry out PTA in the radiological suite, an increasing number of surgeons now perform balloon angioplasty in the operating theatre, either as a primary procedure or as an adjunct to open vascular surgery. A recent sample of 100 members of the Vascular Surgical Society of Great Britain and Ireland revealed that 40 per cent performed some intraoperative angioplasty, a trend that may provoke a number of interesting controversies.

The primary question that must be addressed remains: 'Is there a genuine need for intraoperative balloon angioplasty?' Clearly, the role of such angioplasty will be principally as an adjunct to reconstructive vascular surgery[2]. However, there are probably only three situations where there is a good indication for balloon angioplasty within the operating theatre. The first is the unexpected finding of inadequate arterial inflow to the groin when attempting a planned femorofemoral, femoropopliteal or femorodistal bypass. This should be a rare event if the patient has been properly investigated, with direct aortoiliac pressure measurements when necessary, using the papaverine technique in uncertain cases[3]. When there is doubt regarding inflow, angioplasty should be performed in the radiology suite with PTA if indicated; by doing this not only can the success or otherwise of the proximal angioplasty be properly assessed but the need for further distal reconstruction may be avoided. The possibilities of increased risk of wound infection and slightly increased difficulty of groin dissection surrounding surgery soon after PTA may be overcome either by performing reconstructive surgery immediately after angioplasty or by deferring it for about 3 weeks where possible. It is doubtful whether it is desirable to place the viability of a distal graft at the mercy of the inevitably uncertain outcome of balloon angioplasty combined with open operation. Nevertheless, it is clear that occasionally, particularly at urgent reconstructive surgery, a situation may arise when intraoperative dilatation makes sense.

The second situation where adjunctive balloon angioplasty might be seriously considered is the concomitant performance of superficial femoral or popliteal dilatation after aortoiliac bypass or similar inflow procedure; this might be done to improve run-off and so maximize the benefit of such a procedure[4]. While it is possible to defer angioplasty, there are technical difficulties and theoretical objections to passing an angioplasty catheter through a recently dissected groin. However, a number of workers have recently described a popliteal approach to such lesions that obviates the need for groin puncture. Also, it may occasionally be possible to insert the lower end of an aortofemoral or axillofemoral bypass or the donor end anastomosis of a femorofemoral crossover graft into the distal external iliac artery; this also facilitates later PTA by removing the need for puncture of a dissected groin.

A possible third situation lies in the operative management of acute arterial thrombosis; arterial dilatation may be undertaken after catheter extraction of thrombus[5]. Nevertheless, with increasing acceptance and availability of percutaneous intra-arterial thrombolysis, there is less reason today for immediate operative intervention in such cases than previously. Acute thrombosis is probably best managed by lysis and subsequent PTA of appropriate causative lesions.

There are some valid reasons why vascular surgeons should not universally attempt intraoperative balloon angioplasty. The most compelling of these is lack of adequate training. Insufficient angiology staff and inadequate facilities may also cause problems. It has been suggested that a minimum training period of 1 year is required to become proficient at the procedure. Unlike cardiologists, few vascular surgeons have either adequate training or an elective radiological list for angioplasty. Consequently their

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experience must be limited to those occasions when they attempt balloon angioplasty during open operation. Clearly, techniques such as postangioplasty intraluminal stenting are outside most surgeons' training. In North America, surgeons have rightly been quick to criticize cardiologists for performing percutaneous transluminal peripheral angioplasty. Should we not therefore be equally critical when examining our own practice? If there are no experienced surgical personnel, why not invite the vascular radiologist into the operating theatre[6] to perform adjunctive angioplasty? Lack of on-call vascular radiologists may be a problem for some, but this ought not to be so in regional centres offering vascular surgery. Good cooperation between surgeon and radiologist can only benefit the patient[7]. As vascular surgeons make a plea for increasing specialization and regional centres of excellence, it is vital that we either train ourselves and our protégés in the techniques of balloon angioplasty or ensure the availability of adequate experienced radiology cover.

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Nasogastric intubation and elective abdominal surgery

The use of nasogastric tubes after elective abdominal surgery remains standard practice for many surgeons. Such tubes, however, cause much discomfort and are associated with significant morbidity. This paper reviews the arguments for and against nasogastric intubation, and finds little evidence to support its continued routine use.

Nasogastric intubation is used routinely by many surgeons after both elective and emergency abdominal surgery, for gastric decompression to prevent acute gastric dilatation and to treat ileus, to monitor upper gastrointestinal haemorrhage, to act as a guide to starting oral feeding, and to reduce tension on suture lines, thereby reducing the risk of anastomotic dehiscence. However, the use of nasogastric decompression may result in some morbidity Respiratory complications, gastro-oesophageal reflux, fluid and electrolyte losses, injury to the vocal folds and, not least, discomfort to the patient are all well recognized problems. Some of these complications may even promote continued ileus The potential advantages of nasogastric intubation must be weighed against the potential disadvantages in each case. In this paper the rationale for nasogastric decompression is reviewed and the value of nasogastric tubes in elective abdominal surgery reappraised

History

John Hunter is widely credited with the earliest use of nasogastric tubes In 1790 he used eel skin stretched over whalebone to act as an enteral feeding tube in a patient with bulbar palsy who was unable to swallow[1]. However, 7 years later Alexander Munro claimed that 30 years previously his father had used a flexible tube of coiled wire covered with leather to effect decompression in cattle with excessive fermentation[2]. Such a tube was advocated by Philip Physick in 1800 to wash out the stomach of poisoned patients[3] Decompression of the stomach with a nasogastric tube was described in 1884 by Kussmaul[4] Westerman in 1910 advocated the use of siphon drainage when paralytic ileus had developed secondary to peritonitis[5]. Matas[6] in 1924 and Meyer[7] 4 years later both used gastric tubes for aspiration and fluid administration. After Levin's description in 1921 of his design of nasogastric tube[8], Wangensteen[9] popularized the concept with a series of experiments on its use in small bowel obstruction reported in 1932. Partly because of the ease with which nasogastric tubes can be passed, compared with the construction of a gastrostomy which was a common practice at the time[10], and partly because of the esteem in which Wangensteen was held, nasogastric suction was used thereafter in almost all patients undergoing abdominal surgery.

Many surgeons throughout the world continue to employ routine intestinal decompression after resection and primary anastomosis of the gastrointestinal tract[11]. However, time-honoured surgical practices developed many decades ago are not necessarily appropriate today Preparation of patients before operation, improved anaesthetic agents and techniques, awareness of the electrolytic and metabolic consequences of surgery, control of infection, and improved nursing care have all contributed to altering the nature of the postoperative period such that nasogastric tubes might now be reserved solely for a few specific indications

Rationale for intestinal decompression

Paralytic ileus

Ileus is familiar to all surgeons: after abdominal operation there is a reduction in propulsive activity in the gastrointestinal tract; bowel sounds are diminished and abdominal distension with nausea and vomiting may occur. The condition may predispose to respiratory complications, wound dehiscence and anastomotic leakage. Previously considered to affect the entire gastrointestinal tract, it is now recognized that peristaltic activity is maintained in the small intestine and that diminished motility occurs to a significant degree only in the stomach and colon. In experimental animal models, activity of the small intestine returns to normal within a few hours; early return of motility has been shown in humans by means of radiotelemetry capsules[3,12,13] There is therefore no substantial period of paralysis of the small intestine after operation. Studies of the stomach have confirmed a period of paralysis that lasts 24–72 h according to the type of surgery[14,15]. Colonic motility is also reduced for variable periods after abdominal surgery, and the sigmoid and rectum seem to recover last[15].

The mechanism by which paralytic ileus occurs is unclear. Studies in animals have suggested that it is a consequence of sympathetic inhibition mediated by spinal reflexes, which are initiated by manipulation of the bowel during operation. The length of operation and degree of insult to the bowel have long been held to be proportional to the duration of any subsequent paralytic ileus. However, recent studies suggest that these assumptions may be incorrect: in an investigation into postoperative bowel motility in humans, no relationship was found between duration of operation and severity of ileus[15]. It has been proposed that the afferent side of the reflex which initiates paralytic ileus originates in the parietal peritoneum rather than from afferent nerves in the gut or visceral peritoneum: this would explain prolonged paralytic ileus after retropubic prostatectomy or retroperitoneal trauma. It would also account for the absence of significant ileus after laparoscopic procedures. If confirmed, this concept would render nasogastric intubation after major excisional surgery illogical – at least on the basis of ileus prophylaxis.

The intestinal tract may secrete up to 8·5 litres fluid every 24 h The use of nasogastric tubes is not associated with the removal of a significant proportion of this volume Therefore, the majority of these secretions must continue to be reabsorbed in the small intestine, even in the early period after operation. In the presence of an intact pyloric sphincter, a nasogastric tube is unlikely to decompress more than the stomach alone. The value of nasogastric intubation in preventing abdominal distension must consequently be related to removal of swallowed air Significant amounts of air enter the gastrointestinal tract only with deglutition[16,17] and so gaseous distension should be most easily prevented by reduction of oral intake in the early postoperative period. Indeed, nasogastric intubation may itself promote aerophagia[18].

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Table 1 *Studies on the value of nasogastric intubation after abdominal surgery*

Reference	Year	No. of patients	Type of study	Upper, lower or mixed abdominal surgery	Comments (tube *versus* no tube)
Nathan and Pain[21]	1991	197	Prospective randomized	Mixed elective	Increased sore throat and nausea with tube
Bauer *et al.*[22]	1985	200	Prospective randomized	Mixed	No difference in complications
Dorairajan *et al.*[23]	1985	201	198 patients with tube, three without	Upper	No difference in complications
Argov *et al.*[24]	1980	300	150 consecutive patients without tube, 150 consecutive patients with	Upper	15·0% pneumonia with tube, 1·5% without
Hendry[25]	1962	232	114 Billroth I gastrectomy without tube, 118 vagotomy and pyloroplasty with	Upper	No difference in complications
Miller *et al*[26]	1972	132	Prospective randomized	Upper	Significantly fewer respiratory complications in 'no tube' group
Wolff *et al.*[27]	1989	535	Prospective randomized	Lower	No difference in complications
Reasbeck *et al*[18]	1984	97	Prospective randomized	Mixed	No difference in complications
Racette *et al*[28]	1987	56	Prospective randomized	Lower	Significantly more abdominal distension without tube, but significantly more atelectasis with
Olesen *et al.*[29]	1984	97	Prospective randomized	Lower	Flatus passed earlier without tube No difference in complications
Meltvedt *et al.*[30]	1985	118	Retrospective non-randomized	Lower	No difference in complications
Ibrahim *et al.*[31]	1977	76	53 consecutive patients with tube, 23 consecutive patients without	Lower	No difference in complications
Burg *et al.*[32]	1978	137	Retrospective non-randomized	Lower	No difference in complications
Cheadle *et al*[33]	1985	200	Prospective randomized	Mixed	Increased time to flatus, length of stay and sore throat with tube but less vomiting
Colvin *et al.*[34]	1986	138	Prospective randomized	Lower	No difference in complications

Acute gastric dilatation

Acute gastric dilatation has long been considered a reason for routine use of a prophylactic nasogastric tube The condition is common in patients after significant trauma, the reported incidence is 9 per cent[19]. In such patients, acute gastric dilatation may be complicated by gastric haemorrhage, pulmonary aspiration and prolonged ileus. Dilatation may also occur after an episode of acute pancreatitis, although much less commonly[20]. However, acute gastric dilatation is very uncommon after elective abdominal surgery; of the 2716 patients described in *Table 1*, none developed this condition.

Gastrostomy as an alternative

Gastric decompression, via a nasogastric or gastrostomy tube, remains a useful procedure. Decompression of the acutely dilated stomach, conservative management of small bowel obstruction in the early stages, conservative treatment of a perforated peptic ulcer with localized minimal contamination, and management of upper gastrointestinal haemorrhage to assess rebleeding may all call for nasogastric intubation. Gastrostomy may be associated with fewer minor problems but major complications, including death, have been recorded in up to 6 per cent of patients[35,36]. Gastrostomy also has problems related to removal of the tube and to its replacement if dislodged. Percutaneous endoscopic gastrostomy has, however, simplified the procedure. Gastrostomy is a good alternative to a nasogastric tube for patients at the extremes of life, in whom complications are more common with the latter Chest infections are more frequent in patients over 60 years of age when nasogastric intubation is employed[37]. Excessive salivation with subsequent aspiration pneumonitis is likely to occur with nasogastric tubes in the elderly and in young children.

Gastrostomy has the advantages that it avoids nasopharyngeal pressure and irritation, the cardia is not compromised and patients find it more comfortable. It does, however, carry small risks of fistulation, peritonitis, haemorrhage from the gastrostomy wound, and wound infection if the tube is sited too close to a laparotomy incision[26] It also represents an additional operation. A prospective trial examining 132 patients, who underwent truncal vagotomy and drainage and who were randomized to receive a nasogastric or gastrostomy tube or no tube at all, demonstrated a significantly greater risk ($P < 0{\cdot}05$) of wound infection in those with a gastrostomy than in either of the other two groups. Avoiding either type of tube resulted in a significant reduction ($P < 0{\cdot}05$) in the incidence of respiratory infection and was much preferred by the patients[26].

Tube management

Nasogastric tubes may be left to drain freely, spigoted and aspirated at intermittent intervals, or a combination of free drainage and aspiration may be employed. Intermittent aspiration has the benefit that patency of the tube is tested regularly; the tube may be flushed if blocked or repositioned if displaced If the tube is left spigoted, the chance of allowing escape of gas and decompression of the upper gastrointestinal tract is lost[3]. A drainage bag allows collection of large volumes of gas as well as fluid

Clinical studies

Upper gastrointestinal surgery

A retrospective study of 300 patients who underwent emergency or elective operations on the upper gastrointestinal tract, in which the first 150 received nasogastric intubation and the second 150 did not, demonstrated a tenfold increased risk of pneumonia (15·0 *versus* 1·5 per cent) in the former group[24]. Routine avoidance of nasogastric intubation in a series of 201 patients undergoing gastric drainage procedures alone, or with various forms of vagotomy, resulted in only three (1·5 per cent) subsequently needing a nasogastric tube because of abdominal distension and vomiting; the incidence of severe respiratory infection was only 1 per cent[23]. Low rates of gastric intubation had been reported previously, with an incidence of 3·4 per cent in 118 patients following vagotomy and pyloroplasty and none in 114 after Billroth I gastrectomy[25]. Thus it would appear that a nasogastric tube is rarely required even after truncal vagotomy, a procedure that denervates the upper gastrointestinal tract. Furthermore, most practitioners of highly selective vagotomy do not use a nasogastric tube after operation (D. Johnston, personal communication).

The influence of H_2-receptor antagonists such as cimetidine on nasogastric intubation is interesting. Although a nasogastric tube is associated with a significant increase in the length of time to passage of flatus, bowel action and cessation of intravenous fluids, as well as a significantly greater incidence of postoperative discomfort, cimetidine has not been shown to reduce these problems[33]. The drug does, however, significantly increase the incidence of pneumonia, perhaps by an influence on gastric flora since bacterial overgrowth has been shown[38] to occur at $\mathrm{pH} > 4$.

The patient fasting after operation swallows about 2 litres recoverable air each day and about 600 ml salivary secretions accumulate in the stomach[39]. The fluid is accommodated without difficulty. The volume of air swallowed increases as fluid intake increases and, as long as the latter is restricted, the upper gastrointestinal tract should not be compromised by excessive gaseous intake. There is, therefore, no reason to drain this region. Apprehensive patients tend to be more aerophagic and so more at risk of nausea, vomiting and abdominal distension, some may require nasogastric decompression.

Lower gastrointestinal surgery

The need for a nasogastric tube after elective colorectal surgery is even less convincing than in upper gastrointestinal operations. In a prospective randomized trial of 200 patients who underwent predominantly lower gastrointestinal operations with or without routine nasogastric aspiration[22], no differences were observed in the frequency of complications between the two groups; there were no instances of aspiration pneumonia, anastomotic leakage or wound dehiscence. The rate at which the tube had to be inserted or reinserted was 6 per cent in the 'no-tube' group compared with 5 per cent in the 'tube' group. A retrospective non-randomized study of a consecutive series of 76 patients undergoing colorectal operations (53 with decompression, 23 without) also demonstrated no significant difference in postoperative morbidity rate and length of hospital stay after operation[31]. A similar retrospective study of 118 patients showed not only no difference in mortality and morbidity rates and length of stay, but also that the tube did not reduce the degree of abdominal distension or hasten the time to recommencement of oral fluids or first bowel action[30]. Smaller prospective randomized studies have largely confirmed these results. In particular, nasogastric intubation is associated with increased risk of chest infection[28], later passage of flatus[29] and an incidence of reintubation similar to that needed when an initial policy of non-aspiration is followed.

The largest reported prospective randomized trial, from the Mayo Clinic, involved 1391 patients who underwent elective colorectal operations[27]. A total of 535 patients were considered eligible for entry: 274 received nasogastric decompression and 261 did not. Abdominal distension, nausea and vomiting were significantly more common in patients with no tube ($P < 0{\cdot}05$) and the frequency of subsequent nasogastric decompression was 13 per cent compared with a frequency of reinsertion of 5 per cent in those undergoing routine decompression ($P < 0{\cdot}05$). The incidence of major complications and length of stay after operation were similar. The authors concluded that, despite the increased rate of minor complications, most patients do not require nasogastric intubation after colorectal surgery and that tube insertion should not be used as a routine procedure.

There are no guidelines to predict which patients will require nasogastric decompression. It is possible that those with extensive adhesions, several previous operations or intra-abdominal sepsis (who are often excluded from trials) are at increased risk, but this requires further study. The Mayo Clinic group[27] empirically recommended use of nasogastric decompression in patients with multiple (four or more) serosal tears, gross peritoneal contamination, intra-abdominal sepsis, extensive fibrotic adhesions or operating time >6 h. They also suggested that nasogastric decompression was useful during operation to deflate the stomach if access was difficult, particularly if GoLytely solution (Seward Medical, London, UK) had been used in preoperative cleansing of the bowel. This technique induces excess gas and fluid, which tend to accumulate in the stomach and duodenum and so be present at the start of the operation. Passage of long intestinal tubes on the day before surgery does not increase the extent of intestinal decompression, as assessed at operation, in terms of ease of packing of the small bowel. However, it may reduce pulmonary atelectasis, perhaps because of reduced abdominal distension after operation[34]. No benefit from long tubes has been shown in terms of morbidity after operation.

Complications

Nasogastric intubation is used at the cost of increased postoperative morbidity. The incidence of respiratory complications, such as atelectasis and pneumonia, is increased by tenfold in some series[24]. Nasogastric tubes inhibit effective coughing, allow mucus plugs to accumulate and hence atelectasis and localized pneumonia to develop[40]. The likelihood of pneumonia associated with the use of nasogastric decompression increases with the age of the patient and duration of intubation.

Nasogastric tubes are also unpleasant for the patient: most remember the uncomfortable sensation of 'the tube in my throat' long after they have forgotten other aspects of their operation. The vast majority of patients are unhappy with a nasogastric tube despite the use of mouth washes, nasal or pharyngeal sprays, lip swabs, ice cubes or changing the tube from one nostril to the other. A nasogastric tube may induce vomiting and is associated with nasopharyngeal soreness, otitis or sinusitis. As many as 50 per cent of patients undergoing nasogastric intubation develop radiological evidence of maxillary sinus inflammation and 75 per cent clinical evidence of rhinitis[41]. A nasogastric tube may cause sudden life-threatening bilateral vocal fold paralysis, possibly as a result of paresis of the posterior cricoarytenoid muscles, secondary to infection and ulceration over the posterior lamina of the cricoid. Diabetics who have undergone renal transplantation are particularly at risk[42].

Intubation of the gastric cardia facilitates gastric reflux. It maintains acid in the lower oesophagus as long as there is sufficient gastric acid available to reflux (equivalent to 300 ml 0·1 mol/l HCl), the patient is supine, and the tube is actually in the stomach and not coiled up in the oesophagus[43]. The mechanism of this reflux remains uncertain but interference with intrinsic sphincteric function, failure of the sphincter to close around the nasogastric tube, and the effects of posture in the recumbent patient all contribute. The tube renders the gastro-oesophageal sphincter incompetent and acts as a wick to encourage migration of gastric acid into the lower oesophagus, causing oesophagitis and even eventual stricture. The surface of the tube becomes covered with a thick amorphous biofilm consisting of microcolonies of bacteria within a matrix of exopolysaccharide glycocalyx. Although this matrix contains many dead and dying cells, many of the microcolonies are intact and the presence of yeast cells helps attachment to the tube. Such colonization occurs[44] after the tube has been in place for only 1 day

The tube may become knotted[45], making its removal difficult, dangerous or impossible. It may be incorrectly positioned even to the extent of an intracranial location[46], placement in the sphenoidal sinus[47] or trachea, despite the presence of an endotracheal tube Suction connected to such a tube will evacuate gas from the lungs and prevent effective ventilation[48]. The only sure test of correct placement of a nasogastric tube is the aspiration of gastric content. A tube may perforate the cervical oesophagus at the time of introduction, traverse the mediastinum and come to lie in the lesser sac[49]. Palpation of the tip of the tube by the surgeon at operation may give the mistaken impression that it is positioned in the stomach, but this can be confirmed only by positive gastric aspiration. The tube may become entrapped in a stapled gastrointestinal anastomosis; this preventable and infrequent complication can be managed successfully by endoscopic extraction[50]. Finally, pneumothorax[51], aorto-oesophageal fistula[52] and perforation of the nasopharynx[53] have all been reported as complications associated with nasogastric intubation.

Other indications

Nasogastric tubes have uses other than those already discussed. Recent evidence has highlighted the importance of maintaining the gut barrier to prevent translocation of bacteria. Enteral, as opposed to parenteral, feeding maintains this barrier function in the critically ill patient and fine-bore nasogastric tubes facilitate enteral nutrition in those unable to feed themselves adequately. Similarly, fine-bore nasogastric feeding of infants and small children on chronic ambulatory peritoneal dialysis awaiting renal transplantation will maintain or improve growth[54,55]. A nasogastric tube can permit oral administration of ^{131}I and other medications to uncooperative patients. A probe can be incorporated into the tip of a nasogastric tube to monitor intragastric pH to permit titration against H_2 antagonists This is particularly useful for patients in intensive therapy units who are at increased risk of haemorrhage from stress ulceration[56]. A Salem sump nasogastric tube allows decompression of the distended small intestine during operation[57]

Conclusions

There are few prospective studies in the literature regarding routine nasogastric intubation in elective abdominal surgery. The use of tubes has been based on anecdotal evidence and the teachings of our forebears· surgeons as pre-eminent as W J. Mayo and A. J. Ochsner have suggested that a nasogastric tube rather than a stethoscope should be carried around the neck of a resident. However, in contrast to the use of nasogastric tubes in acute conditions, their continued use in elective abdominal surgery is no longer justified. It is safe to omit intubation as long as oral fluids are restricted until flatus has been passed[32]. A small proportion of patients will subsequently require intubation on the basis of clinical signs such as persistent vomiting or abdominal distension. No harm should come to patients if they are allowed to select themselves, rather than be at the receiving end of a blanket policy.

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Review

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Function of the human colon

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Despite the volume of research on human colonic dysfunction, little is known about colonic function in health. This has stemmed partly from the difficulty in obtaining access to the organ. Two approaches have been used: studies on patients with stomas, and intestinal intubation techniques. The colonoscope has also recently been used to gain access. All these methods have limitations and results must be interpreted with caution. The accepted roles of the colon include the conservation of water and electrolytes and the controlled evacuation of faeces. Recent research has demonstrated its importance as a metabolic organ with an influence on overall metabolism, an effect that may in large part be attributed to the activity of colonic microflora. Evidence demonstrating that the defunctioned colon behaves differently from the functioning colon in the same individual has implications for a proper understanding of the organ, as practically all previous in vivo *studies have been conducted in cleansed or defunctioned human colon.*

Medical science has traditionally taken a limited view of the function of the human colon. The large intestine has been considered a useful, albeit dispensable, organ for conservation of salt and water, and a reservoir for faecal storage and controlled evacuation. Anatomically, the colon is a muscular tube approximately 150 cm long extending from the ileocaecal valve to the rectum[1,2]. The volume of the luminal contents, or capacity of the colon, is variable and can be negligible (for example after bowel preparation for surgery) or the organ may contain a vast amount of stool in individuals with chronic constipation. In the normal individual the colon contains somewhere in the region of 220 (range 58–908) g of contents[3,4]. The metabolic activity within the lumen of the colon has been largely disregarded and has generally been considered detrimental to the host. In particular, the activity of the resident microflora, which collectively outnumber the individual's own cells[5], has received little attention.

Since the early 1970s, epidemiological observations linking bowel habit and fibre intake with a broad spectrum of diseases have focused attention on colonic function[6,7]. One result of this increased interest has been the suggestion that the colon is an important organ with influences on overall body metabolism[8,9]. Removal of the colon may, therefore, have general implications for overall well-being.

A major barrier to understanding colonic function has been the relative inaccessibility of the intact functioning organ. To circumvent the problem, two main approaches have been adopted. The original method was the study of surgically created stomas. In many instances, this has been superseded by the use of intestinal intubation techniques. This review outlines the methods of assessment and the current state of knowledge of the role of the human colon, and extrapolates some ideas on function by analysis of areas of colonic dysfunction.

Assessment of colonic function

Intestinal stomas

Ileostomy as a model of colonic influx. Ileostomy output has been studied on the assumption that it approximates to, or is representative of, the normal efflux from the ileum into the colon[10–13]. However, following the construction of an ileostomy there are major changes in function. For example, the daily fluid output of an established ileostomy[14,15] is of the order of 300–500 ml, whereas intubation studies[16] have demonstrated that normal daily efflux from the intact ileum to the colon is approximately 1500 ml. This implies that there is increased absorption and/or decreased secretion by the small bowel of patients with an ileostomy.

One important change that takes place when the ileum is exteriorized as an ileostomy is that the terminal ileum becomes colonized with bacteria. Normally the ileum contains very few organisms and over 99·9 per cent of the gastrointestinal flora are confined to the colon[5,17]. Vince *et al* [18] found that within 24 h of ileostomy formation the ileal flora changed substantially, with colonization by a large number and variety of organisms. Gorbach *et al.*[19] showed that the effluent from an established ileostomy contained approximately 80 times the number of organisms per unit weight than did normal ileal contents, faeces contained 25 times as much again (*Table 1*). The combined effect of microfloral proliferation together with changes in fluid output demonstrate that an ileostomy effluent is unlikely to model normal colonic inflow accurately. Although useful observations have been made from the study of patients with an ileostomy, caution has to be exercised in extrapolating results to normal colonic influx.

The observation that patients can maintain reasonable health after colectomy[20] has been taken to imply that the human colon has no important metabolic function. An alternative perspective is that the colon with its normal flora is an important metabolic organ[8,9], and when it is removed the bacterial colonization of the exteriorized ileum assumes some of its metabolic functions, thereby helping to maintain well-being. Such compensation might be expected to be limited, and recent evidence suggests that patients with an ileostomy

Table 1 *Comparison between ileal and stoma efflux, and stool*

	Output per day		
	Water (ml)	Micro-organisms ($\times 10^6$/g)	References
Intact ileal efflux	1500	1	2, 15, 16, 19
Ileostomy efflux	500	80	14, 15, 19
Transverse colostomy efflux	300	80	15, 21
Normal stool	100	2000	2, 15, 19

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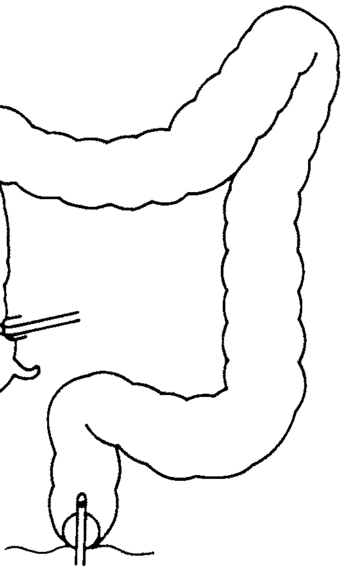

Figure 1 *Perfusion of the intact human colon after orocaecal intubation with a long intestinal tube. The effluent is collected via a Foley catheter (with the balloon inflated), which is positioned in the rectum*

do have a reduction in total body nitrogen and potassium[21]. Cooper *et al* [21] concluded that loss of the colon was associated with a reduction in fat-free mass and, therefore, a degree of subclinical malnutrition.

Colostomy as a model of colonic function The exteriorization of the colon as a colostomy on the anterior abdominal wall is a relatively common procedure and, although the colon is not normal in this state, any diseased segment has usually been removed. In general, colostomy effluent is less fluid than that from an ileostomy but more fluid than faeces[15]. Similarly, colostomy effluent has a bacterial content greater than that of ileostomy effluent but less than that of faeces[22]. A colostomy might be expected to reflect more closely the function of the intact colon than extrapolation from ileostomy studies, but relatively little work has been performed using colostomies; this approach has potential for widening our understanding of some aspects of colonic function[23–25].

Intestinal intubation

Intubation techniques have provided much information on colonic function Such methods were originally introduced for measuring the length of the small intestine and for sampling intestinal contents at various levels[26] The technique involves passing a long tube from the mouth into the small or large intestine. The tube is initially positioned in the duodenum under radiographic control; a balloon at the end is then inflated and peristalsis carries the tube through the small bowel. The position is confirmed radiologically. The tip of the tube is usually positioned in the caecum (orocaecal intubation); proximally located lumens may be used for either perfusion or sampling.

Levitan *et al.*[27] were the first to use this technique in a detailed study of salt and water absorption by the human colon; the method has since been adopted by several other groups. After intubation of the caecum 'the colon was cleansed thoroughly by perfusing it with normal saline until the material expelled rectally was clear and relatively free of mucus'[27]. Cleansing of the colon was felt to be the only way of establishing a steady-state perfusion model to allow calculation of function After the cleansing period, 2 h were allowed for subjects to expel or absorb the saline remaining in the colon before the perfusion study commenced. The perfusate was infused at 10 ml/min and the effluent collected distally, usually by a urinary catheter (with the balloon inflated) placed in the rectum (*Figure 1*). The net absorption or secretion by the colon could be calculated once a steady-state perfusion had been achieved. This technique has some limitations. The volume perfused[16] at 10 ml/min is equivalent to 14 400 ml/day, much greater than the normal colonic inflow from the ileum of approximately 1500 ml/day Furthermore, the normal intestinal transit time is of the order of 60–72 h, 40–60 h of which are spent in the colon[9]. Nevertheless, important information has been obtained from perfusion studies, such as the large reserve capacity of the colon and the knowledge[28] that the organ can absorb up to 5700 ml water and 816 mmol sodium per day.

Colonic metabolism

There has been little research into the basic roles of the normal colon and few have attempted to define and categorize such functions. Indeed, much of our knowledge has resulted from extrapolation from research into colonic dysfunction. For the purposes of this discussion, human colonic function may be grouped into three broad categories

1. A capacity function, to absorb water and electrolytes, and to store and evacuate stool.
2. A reservoir function for bacterial metabolism and fermentation.
3. A metabolic function with complex effects on overall body metabolism.

In many instances these functions overlap and are inter-related; for example, alterations in the colonic flora may result in disorders of water and electrolyte absorption culminating in diarrhoea. Nevertheless, it is worthwhile, in the first instance, exploring colonic functions individually

Colonic capacity: water and salt absorption

The daily influx of water to the caecum[16] is of the order of 1500 ml As stool water[2,3,15] is approximately 100–200 ml/day, approximately 1300–1400 ml is absorbed. However, there is a reserve capacity and there has been considerable research to establish the maximum absorptive capacity of the colon and the factors that affect it. Debongnie and Phillips[28], using an orocaecal tube, infused an additional 2000 ml into the caecum with little change in stool weight or frequency. They calculated that the colon could absorb 5700 ml water, 816 mmol sodium and 44 mmol potassium per day. It was shown that the rate and pattern of fluid entry were important, as 500 ml isotonic electrolyte solution infused over 1 h resulted in diarrhoea, whereas 167 ml/h infused at a steady state over 24 h (4000 ml in 24 h) could be absorbed.

The colon as a reservoir for bacterial metabolism and fermentation

The colon is a reservoir for 99·9 per cent of the human gastrointestinal microflora[5,19]. Colonic flora are composed of over 400 different species and collectively outnumber an individual's own cells[5]. Colonic bacteria or bacterial products can be lethal if the colonic mucosal barrier is breached, a balance thus exists between the host and a vast number of potentially lethal bacteria The colonic microflora are predominantly anaerobic[5,17] and ferment carbohydrates, with the production of short-chain fatty acids (SCFAs). The carbohydrate available for fermentation in the colon comes from endogenous sources, such as mucus, and exogenous dietary sources that escape digestion in the small intestine. The dietary sources are varied and complex. Some dietary starch is digested, whereas resistant starch is not. Non-starch polysaccharides, loosely referred to as fibre, are not susceptible to digestion and pass through the small intestine[29].

The main SCFAs are acetate, butyrate and propionate, all of which have been shown to stimulate growth of the colonic mucosa[30] Butyrate, in particular, has a trophic effect and is the preferred substrate for colonocytes[30]. Removal of fibre from the diet results in atrophy of the mucosa of the small intestine and colon; colonic atrophy can be reversed by the infusion of SCFAs into the colon[30,31] and, surprisingly, such infusion also corrects the atrophy of small bowel mucosa[31]. This suggests that absorbed SCFAs can exert a systemic effect at distant sites. Disorders of SCFA metabolism have been implicated in colonic mucosal diseases, especially in inflammatory bowel disorders such as Crohn's disease, ulcerative colitis and diversion colitis[30]. Production of SCFAs alters colonic pH and increases colonic motility[30]. There is thus evidence to suggest that bacterial fermentation may play a direct role in colonic mucosal function and also more generally in metabolism

Factors that exert an effect on fermentation by the colonic flora appear to modify the absorptive capacity of the colon Rao *et al.*[32] found that, when subjects on a normal diet were given 2 g/day ampicillin, 36 per cent developed loose stools The same subjects had no change in stool weight or frequency when taking 20 mg/day lactulose However, when both lactulose and ampicillin were given, 84 per cent of subjects had diarrhoea and all had significantly increased stool weight and frequency. Diarrhoea is a recognized side-effect of many antibiotics and this is especially true of the broad-spectrum types Keoghane *et al* [33] have shown that practically all patients who develop diarrhoea on enteral feeding are also on concomitant antibiotics. Thus, it seems probable that antibiotic-associated diarrhoea results from interference with the normal metabolism of the colonic microflora.

The colon as a metabolic organ with effects on overall metabolism

Evidence is accumulating to support the importance of the colon in overall body metabolism. However, this is most likely to be an effect of colonic bacterial metabolism, rather than of colonic function *per se*. Some of the roles of SCFAs have already been addressed and these may prove to have widespread effects[2,30]. Few have considered that the colon plays a part in human nutrition, although Jackson[8] has provided evidence that it may be important in nitrogen conservation. Furthermore, a recent study has demonstrated the importance of the colon in nutrient absorption in patients with very short lengths of small intestine (short bowel syndrome)[34]. Nightingale and colleagues[35], who had previously confirmed the role of the colon in salt and water absorption, went on to demonstrate that patients who had their short gut in circuit with the colon had far superior nutrient absorption than those whose small intestine ended in a stoma[34] It is possible to calculate from their results that the colon in circuit has a functional capacity in nutrient absorption similar to that of 50 cm of jejunum. This remarkable finding goes against the orthodox teaching on colonic function, which has been that the organ can absorb water and electrolytes but that all nutrients in faeces are lost. There is also recent evidence to support the role of the colon in human nitrogen metabolism, which will be addressed below[8,23–25,36,37].

Colonic dysfunction

Considering the dearth of knowledge on specific functions of the normal colon, a vast amount of research has focused on aspects of its dysfunction, which has been categorized into two broad divisions

1. Disorders of motility – mainly constipation and diarrhoea, but also irritable bowel syndrome and diverticular disease.
2. Colonic mucosal diseases – polyps, carcinoma, inflammatory bowel disease and colonic infestation

For clinical diagnosis, the barium enema has been the most important investigation of colonic dysfunction, and the recent introduction of fibreoptic colonoscopy has revolutionized diagnosis and management, especially of mucosal disease[38]. Colonoscopic biopsy allows histological confirmation of previously inaccessible lesions, and polyps can be removed without recourse to surgical intervention. Colonoscopy has also provided access to hitherto inaccessible parts of the colon for research studies[36,39] Thus, whereas pressure and voltage studies could traditionally be performed only in the rectosigmoid region, it is now possible to position probes at any site in the colon[39] Despite these advances there has been little real progress in defining basic colonic function. Nevertheless, many studies of dysfunction provide useful insights; in particular, studies of diarrhoea, colonic motility and colonic nitrogen metabolism have been enlightening These are covered in the following sections.

Diarrhoea

Normal stools are the result of complex interactions between dietary residue, water and electrolyte secretion and absorption, secretion of digestive enzymes and juices, mucus formation, sloughed cells, intestinal motility and the metabolism of the colonic flora. A number of factors affect salt and water absorption in the colon. The effect of bile salts has been extensively studied; infusions of these into the colon reduce net absorption of water and may induce secretion[28,40,41] As bile salts are normally absorbed in the terminal ileum, this may partly explain the diarrhoea that frequently accompanies ileal disease. Infusion of oleic acid into the caecum causes a marked reduction in colonic capacity and an increase in transit time[42].

Diarrhoea is a common sequel to partial or subtotal colectomy Although it is difficult to predict which patients will suffer from diarrhoea following colectomy, work by Cummings *et al.*[43] suggests that both the absolute amount and functional ability of the residual colon are important In patients suffering from diarrhoea after ileocolic resection, severity of diarrhoea and faecal weight are proportional to the length of colon resected and much less influenced by the length of resected ileum[43]

In summary, diarrhoea can be regarded as a malabsorption of the fluid that normally enters the gut both in the diet and from intestinal secretions The large reserve capacity of the colon[28] may be overcome in a variety of ways, resulting in diarrhoea[28,32,33,40,42,44].

Colonic motility

Constipation, diverticular disease and irritable bowel syndrome account for the majority of adult colonic motility disorders Intestinal motility can be assessed with radio-opaque markers[45]. Another approach has been to follow the movement of a bolus of ^{111}In-labelled diethylenetriamine penta-acetate instilled into the caecum. Using this technique, it has been suggested that the transverse colon is the main storage site for faeces[46], which would explain why few patients develop diarrhoea after right hemicolectomy, but a recent report suggests that the right colon is the storage area[42]

Disturbances in pressure have been suspected as being important in motility diseases, but measurements of pressure have been hindered by the inaccessibility of much of the colon As pressure transducers can now be positioned using a colonoscope[39], it is likely that measurements of this kind will further our understanding of some conditions that have so far been labelled as irritable bowel syndrome for lack of a more definitive diagnosis.

Constipation is a common symptom (even if difficult to define), affecting as many as 10 per cent of the general population[9]. It is often a feature of, and difficult to separate from, other motility disorders such as diverticular disease and irritable bowel syndrome In all three, transit time is prolonged and intraluminal pressure raised[47]. However, patients with constipation tend to have a more prolonged increase in transit time, whereas those with irritable bowel syndrome have more pronounced pressure increases. Patients with diverticular disease fall into both categories[47].

Patients with motility disorders have detectable abnormalities in transit time and intraluminal pressure, but the pathophysiology of these disorders is largely unknown. There is epidemiological evidence linking many motility disorders to a relative lack of dietary fibre[6] and the effect of fibre on transit time and stool weight appears to strengthen this hypothesis[7,48,49]. Although dietary fibre is useful in the treatment of constipation, it is notable that those who are constipated generally require more fibre than normal subjects to increase stool weight by a similar proportion[9]. Idiopathic slow-transit constipation is resistant to treatment with dietary fibre This is predominantly a disease of young women and appears to be a disorder of colonic motility with an inability to evacuate normally[50]. In a true case of intractable constipation the only effective treatment may involve the radical step of total colectomy. Sensitive and specific preoperative investigations are essential to select appropriate candidates for what is a major irreversible procedure. Roe and colleagues[51] recently evaluated 74 patients with intractable constipation to assess which investigations would be most valuable in predicting benefit from surgery. Transit time and defaecation proctography emerged as the most useful. Eight patients with severe slow transit underwent colectomy and five of these had a good result. Rectal intussusception was seen in 13 of 35 proctograms. Again, eight patients underwent surgery, in the form of rectopexy, but in only three was the condition improved.

There are qualitative differences in types of dietary fibre, and both particle size and chemical composition of the individual polysaccharides affect the mode of action with respect to the colon[9]. Preparations with greater particle size produce larger changes in stool output[52,53]. This suggests that the particles themselves may stimulate the colonic mucosa, a theory that is supported by the recent demonstration of a laxative effect of indigestible plastic particles[54]. The chemical composition of the fibre polysaccharide determines its degree of fermentation by colonic microflora, when equal doses of cabbage and bran were given to normal subjects, only 10 per cent of the cabbage was recovered in the stool compared with 60 per cent of the bran[55].

The effect of fibre can be broadly divided into two categories: the insoluble fibres (such as bran) hold water and act as a bulking agent; and the soluble fibres (such as cabbage and ispaghula) are fermented by bacteria and promote bacterial proliferation This proliferation results in an increase in stool weight, as bacteria are 80 per cent water and account for up to half of faecal solids[9].

Nitrogen metabolism

The metabolism of nitrogenous substances in the colon has been considered clinically relevant in renal failure and hepatic encephalopathy. In patients on a low-protein diet for renal failure, hydrolysis of urea by the colonic microflora provides a potential mechanism through which the load to be excreted by a diseased kidney is reduced. The functional relevance of this mechanism has been disputed.

In liver failure the production of ammonia and other nitrogenous substances by the microflora in the colon contributes to hepatic encephalopathy[56]. The demonstration that blood draining the colon has a much higher ammonia content than that from other segments of the bowel provides evidence for the involvement of the microflora in ammonia generation The level of ammonia in blood from the colonic veins is ten times that in the inferior vena cava; the concentration may be reduced by 65 per cent by oral antibiotics[57].

There is confusion about the way in which nitrogen is handled in the lower bowel, individual investigators having reported findings that seem mutually incompatible. Walser and Bodenlos[58] established that a significant proportion (20–30 per cent) of the daily production of urea was hydrolysed in the body and that this was through bacterial hydrolysis in the colon. Summerskill and Wolpert[59] estimated that 75 per cent of the ammonia production in the gastrointestinal tract was colonic and, as the 3 8 g ammonia produced daily could derive from the known hydrolysis of urea, they concluded that a major source of ammonia might be the hydrolysis of urea. However, insufficient nitrogen enters the colon from the ileum to account for the known colonic ammonia production[10,14,60], which suggests that a substantial proportion of the nitrogen that goes to form ammonia must pass through the colonic wall in the form of urea and other nitrogenous substances[8].

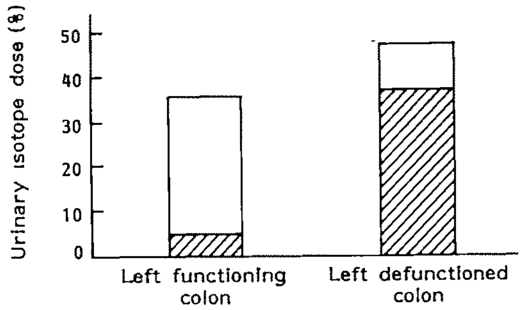

Figure 2 *Differences between the functioning and defunctioned colon Urinary recovery of* $[^{15}N]$*urea* (□) *and* $[^{15}N\,^{15}N]$*urea* (■) *after instillation of* $[^{15}N\,^{15}N]$*urea into the lumen of the left functioning colon* (*in patients with a left end colostomy*) *compared with that after instillation into the left defunctioned colon* (*in patients with a defunctioning colostomy*). *The differences are statistically significant* ($P < 0\ 01$, *Wilcoxon rank sum test*)

There has been controversy too about the site of urea hydrolysis, but the demonstration that $[^{15}N\,^{15}N]$urea placed directly in the colonic lumen may be either rapidly hydrolysed or absorbed directly confirms that the human colon is permeable to urea and that urea hydrolysis occurs within the lumen of the organ[24,25,36,37]. Significant proportions of hydrolysed urea nitrogen are retained within the body pool, indicating that nitrogen from hydrolysed urea is available and used for metabolic interaction.

The authors have examined colonic nitrogen metabolism using two groups of patients: one with a left iliac fossa end colostomy and the other with a defunctioning colostomy. Separate studies compared functioning and defunctioned colon in the same individual[24,25]. Comparisons were also made between the left defunctioned limb in one group and the functioning left-sided end colostomy in the other; it was concluded that the defunctioned colon behaves in a different manner to the functioning organ (*Figure 2*). If this is so, much of the research into colonic function, which has been carried out on the defunctioned or cleansed colon, may require re-evaluation

Anatomical and functional differences between regions of the colon

The extent to which there are functional differences between the right and left colon has not yet been fully resolved. Embryologically, the junction between the midgut and hindgut is in the distal third of the transverse colon, with the superior mesenteric vessels supplying the midgut and the inferior mesenteric the hindgut[1]. In most mammals the midgut and hindgut are separated by a sphincter or valve[61]. Although a valve or sphincter has not been demonstrated in humans, recent studies of colonic motility have demonstrated a difference between the right and left colon and imply a functional sphincter somewhere along the transverse colon[42] Others have suggested that the whole transverse colon may act in a valve-like manner[46]. There certainly appear to be metabolic differences between the right and left colon[2], but their exact significance is uncertain.

Colonic function interactions

While considering the individual functions of the colon, it must be remembered that all these interact. Central to all aspects is the role of bacterial fermentation, which may be the primary role of the colon and, as a consequence, make it a metabolic organ in its own right[8]. An example of these complex interactions has been explored by Cummings and Branch, who demonstrated that an increase in intake of fermentable dietary fibre results in an increase in stool bulk and an increase in stool nitrogen with a decrease in stool ammonia[62]

The ability to live a relatively normal life after colectomy[20,63] tends to discredit the hypothesis that the colon has an important metabolic function However, if the normal ileal efflux[16] of 1500 ml/day were to continue after removal of the colon, colectomy would result in a daily net loss > 1000 ml In fact, the daily output from an established ileostomy[14,64] is 300–500 ml, showing that adaptation occurs The adaptive mechanisms have received little attention but may involve microfloral colonization of the ileostomy and terminal ileum[19,22]. It may well be that this bacterial colonization of the ileum takes over some of the metabolic functions of the colon.

Colonic function has been so dismissed that it has been suggested that a patient with a tumour localized to one side of the colon may best be treated by total colectomy with ileorectal anastomosis[64] Marston has argued that total colectomy rules out the possibility of a further colonic tumour, but admits that loss of the colon 'results in a varying degree of diarrhoea and frequency which cannot always be controlled by diet and drugs'[64] With our current paucity of knowledge of colonic function this radical viewpoint may be unjustified[37].

Conclusion

It has been succinctly stated that 'I have known the happiness of a whole household to hang daily on the regularity of an old man's bowels'[65], yet there has been relatively little research into the function of the colon. Recent evidence suggests that the little we know may be less than accurate There is a need to address the following. the precise functions of the intact colon; the metabolic consequences of removal of part or all of the colon; the role of colonic microflora in health and disease and the consequences of alterations in the flora, the anatomical functional differences; and the precise role of the products of fermentation in health and disease.

Until this information is available, every effort should be made to preserve as much of the normal human colon as is reasonably possible. Current evidence suggests that the human colon is far from being a mere conduit and that its role in health and disease has been underestimated.

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Mycetoma

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Mycetoma is a chronic infective condition of tropical and subtropical regions. It is commoner in males, especially those in their third or fourth decade who work on the land. The clinical triad of subcutaneous nodule, sinuses and discharge usually leads to diagnosis; the disease is commonly painless. Treatment is by extensive surgical excision of affected areas and may include limb amputation. Recurrence is common, rates ranging from 20 to 90 per cent. Medical treatment may be used on its own or as an adjunct to surgery. Although such therapy may cure over half of those with actinomycetoma (caused by bacteria, mainly aerobic actinomycetes), those affected by eumycetoma (caused by fungi) have a poorer prognosis and may require many years of drug therapy.

Mycetoma is a chronic subcutaneous granulomatous lesion caused either by true fungi (eumycetoma) or by higher bacteria, mainly aerobic actinomycetes (actinomycetoma)[1]. It was first described by Gill of Madura in south India in 1842, hence the name 'madura foot'. In 1860 Carter introduced the term mycetoma ('fungal tumour') to indicate the origin of the disease[2]. Although it has a worldwide distribution, mycetoma constitutes a major health problem primarily in tropical and subtropical regions[3]. It is endemic in the mycetoma belt between latitudes 15°S and 30°N, which includes Sudan, Somalia, Senegal, Mexico, India, and Central and South America[4–7]. Areas where mycetoma is endemic have a short rainy season of 4–6 months with a relative humidity of 60–80 per cent and a fairly constant temperature of 30–37°C both day and night, followed by a dry season of 6–8 months with a relative humidity of 12–30 per cent, a day temperature of 45–60°C and a night temperature of 15–18°C[8,9]. The disease has also been reported in areas of temperate climate[10,11]. Conservative estimates of the incidence of mycetoma in the Sudan vary from 300 to 400 new hospital cases annually[8]. This figure does not take into account the considerable number of outpatients and those seen at peripheral dispensaries where qualified doctors might not even be present. Although studies on patients with mycetoma have indicated a deficiency in cell-mediated immunity, there has been no report of the effect of the spread of human immunodeficiency virus infection in Africa on the incidence of the disease.

Eumycetoma is caused by a variety of fungi, including *Madurella mycetomi*, *M. grisea* and *Pseudoallescheria*, while actinomycetoma is caused by *Actinomadura madurae*, *A. pelletieri*, and species of *Nocardia* and *Streptomyces*[12,13]. The causal organism is usually found in the soil and enters the host through a breach in the skin or the mucosal membrane caused by sharp objects such as a thorn. The disease is not contagious. Its incubation period is unknown because of difficulty in determining the time of initial infection. However, in experimental animals the development of mycetoma has been noted[14,15] after an incubation period of 3 weeks.

Clinical presentation

Mycetoma is five times commoner in males than females and generally occurs in adults between 20 and 40 years of age, although in endemic zones children and the elderly may also be affected[16]. No occupation is exempt, but the disease typically affects cultivators, field labourers and herdsmen.

The clinical triad of subcutaneous nodule, sinuses and discharge is diagnostic (*Figure 1*). Mycetoma usually presents as a slowly progressive painless nodule at the site of previous trauma, commonly in the dorsal aspect of the forefoot; this occurs in 70 per cent of cases (*Figure 2*)[17]. The hand, affected in 12 per cent of cases, is the next commonest location (*Figure 3*); in endemic areas other rarer sites may be affected e.g. the thigh, orbit, air sinuses, testes, ear and mandible[18–20] (*Figure 4*). The subcutaneous nodule gradually increases in size and multiple secondary nodules may develop, suppurate and drain through multiple sinuses that may temporarily close. These sinuses are usually connected with each other, and with deep sterile abscesses and the skin. They show very little tissue reaction at their cutaneous openings[21,22]. The discharge is usually serous, serosanguinous or purulent. Quite often the pus associated with mycetoma is sterile; this is probably the effect of antibiotics produced by the mycetoma itself[23]. Staphylococci or streptococci may occasionally be isolated. During the active phase of the disease, the sinuses discharge grains of a colour that depends on the type of organism; they may be black (*M. mycetomi*), white (*A. madurae*), red (*A pelletieri*), or yellow (*S. somaliensis*). The grains are of variable size and consistency[24].

The clinical picture of mycetoma is almost uniform, irrespective of the causal species. The organism multiplies in the subcutaneous tissue, forming colonies that spread along fascial planes to involve skin, deep structures and bone. It eventually causes bone destruction with cavities and deformity; tendons and nerves are usually not affected[25]. In eumycetoma the lesion grows slowly and remains encapsulated for a long time, whereas in actinomycetoma it is more aggressive, more destructive and involves bone at an early stage[26,27]. In 1–3 per cent of cases there is genuine lymphatic spread of mycetoma to regional nodes; this type of spread is more common with actinomycetoma. Other causes of enlarged regional lymph nodes are secondary bacterial infection or local immunological reaction to the disease[28].

Although mycetoma is generally painless, in about 18 per cent of patients it is painful because of secondary bacterial infection or, in some cases, bone expansion by the mycetoma[29]. Constitutional symptoms and signs are rare, but when they occur generally result from secondary bacterial infection of open sinuses. Lymphoedema and varicose veins are rarely observed in infected patients. The disease is rarely fatal but produces disabilities and deformities in its later stages[30]. Primary osseous mycetoma without soft tissue involvement is sometimes encountered; the route of infection is unclear. There is no report of blood-borne spread of the disease.

The radiological features of mycetoma are interesting. In the early stages there may be a soft tissue mass with obliteration of fascial planes. Bone cortex may be compressed from outside by the mass, producing scalloping which is followed by a

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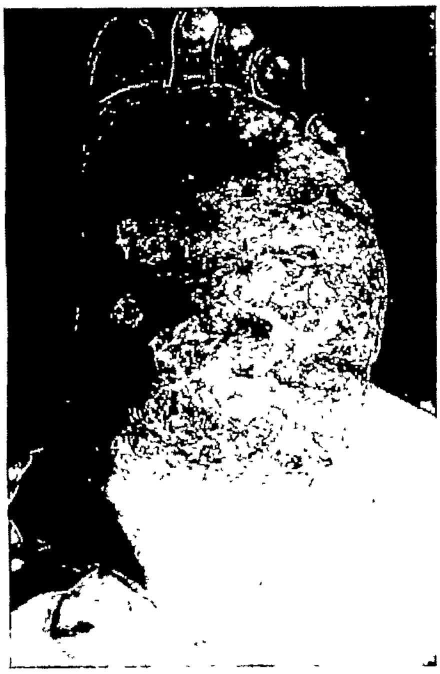

Figure 1 *Mycetoma foot with the triad of a mass, sinuses and discharge*

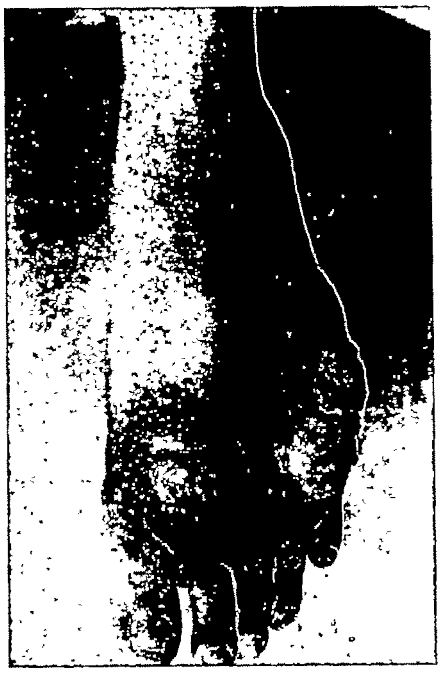

Figure 2 *Mycetoma involving the dorsal aspect of the forefoot*

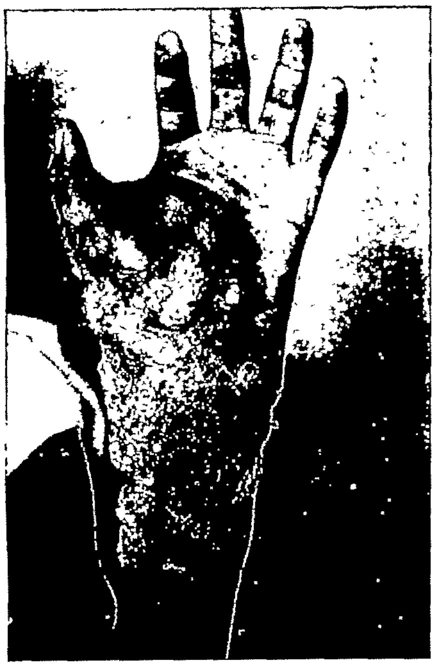

Figure 3 *Eumycetoma involving the hand and forearm with multiple healed sinuses*

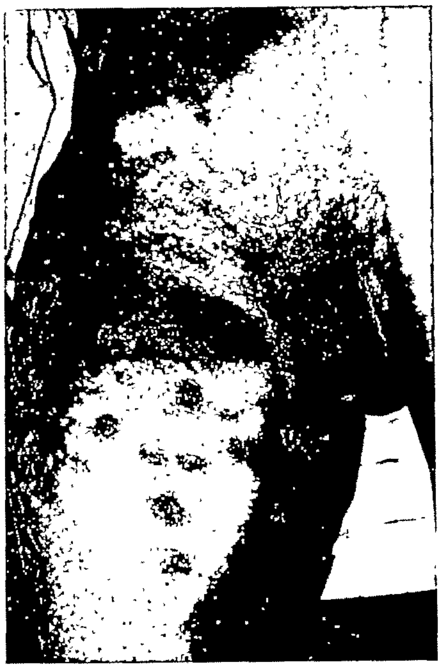

Figure 4 *Actinomycetoma involving the upper thigh and the lower part of the anterior abdominal wall*

variable amount of periosteal reaction. Sunray appearance and a Codman's triangle may be present, producing a picture similar to that of osteogenic sarcoma (*Figure 5*). There may be multiple cavities within normal-density bone. These cavities are large, few in number, and in eumycetoma have well defined margins (*Figure 6*). In actinomycetoma they are small, numerous and their edges ill defined (*Figure 7*). The size of the cavities is a function of the size of the grains[31]. Osteoporosis is common in late mycetoma due to disuse atrophy and to pressure on blood vessels supplying the bone. Pathological fractures are unknown, because bone is replaced by grains, giving the bone some support[32].

The differential diagnosis includes soft tissue swellings such as thorn granuloma, fibrolipoma, neurofibroma, Kaposi's sarcoma and malignant melanoma. Osteogenic sarcoma and bone tuberculosis may have similar radiological appearances to mycetoma but sequestration does not occur in mycetoma. Primary osseous mycetoma must be differentiated from chronic osteomyelitis, osteoclastoma and syphilitic osteitis[33,34].

Diagnosis

The condition is usually diagnosed clinically. Confirmation is possible by demonstrating significant levels of antibodies against the different types of causal organisms by counter-immunoelectrophoresis, immunodiffusion or enzyme-linked immunosorbent assay[35–39]. Histological examination of the surgical specimen using haematoxylin and eosin or periodic

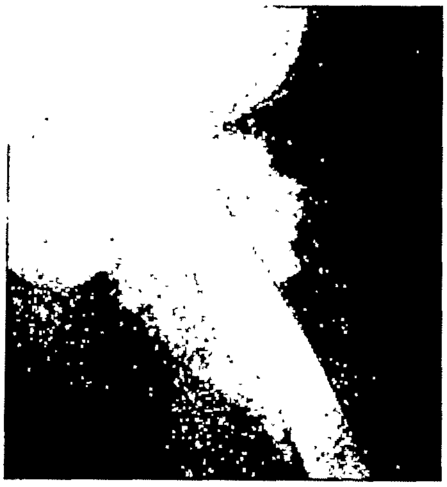

Figure 5 *Radiograph of the femur of a patient with actinomycetoma showing periosteal reaction, new bone formation and sunray appearance*

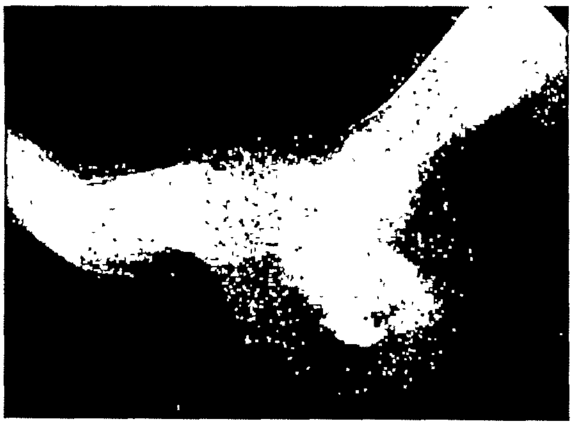

Figure 6 *Radiograph of foot showing a big cavity in the calcaneum with well defined edges and sclerosis typical of eumycetoma*

acid–Schiff stains can identify the causal organism and demonstrate the type of local tissue reaction against it[40,41]

Surgical treatment

Surgery for mycetoma ranges from local excision to mass reduction and occasionally to amputation of an affected limb. The aim of such treatment is complete removal of the lesion. This is possible in about 30 per cent of patients who have early disease in which the granuloma is localized. Actinomycetoma has ill-defined limits, so a wide margin of healthy tissue should be excised with the lesion if possible. Great care must be exercised during surgery to minimize the spread of grains along fascial planes if recurrence is to be avoided. The surgeon should not cut across the lesion or see the grains; a bloodless field, using a tourniquet, is mandatory. Some authorities advise flooding the wound at the end of the procedure with iodine solution to destroy any missed grains, but there is no firm evidence to support this technique. Surgical mass reduction of a lesion that cannot be completely excised greatly facilitates the response to medical treatment. Approximately one-quarter of all mycetomas require amputation of part or all of the foot and, rarely, of the hand[17]. To avoid the socially disastrous consequences of amputation, a programme of extensive repeated excision of diseased tissue, including bone, may be carried out preferentially[42]. Such debulking procedures are carried out in about one-fifth of patients. The recurrence rate after surgical treatment is high, ranging from 20 to 90 per cent[43]. Medical treatment before and/or after surgery may be used in certain circumstances[44].

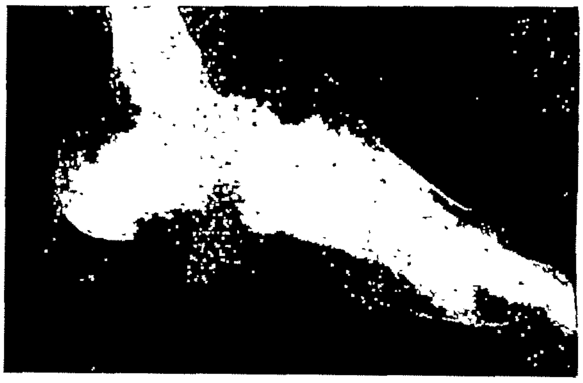

Figure 7 *Radiograph of foot showing advanced actinomycetoma with multiple small cavities with ill-defined edges*

Medical treatment

Medical treatment alone or in combination with surgery is used in about one-quarter of patients. It is indicated for those with massive or inoperable lesions, and in those with recurrent lesions after surgery. It is more effective in actinomycetoma than in eumycetoma; the latter may produce a cement substance around the organisms demonstrable by ultrastructural studies. Many drugs and drug combinations have been tested both *in vivo* and *in vitro* against mycetoma pathogens. Mahgoub[45] reported 144 patients with actinomycetoma treated medically; 63 per cent were cured, 22 per cent enjoyed great improvement, and 11 per cent showed some improvement. Treatment may be successful even when there is bone involvement[46]. In patients with actinomycetoma, medical treatment consists of dapsone 100 mg twice daily and streptomycin 1 g daily for 1 month. The streptomycin dosage is then reduced to 1 g on alternate days[47]. If the response is not satisfactory dapsone is replaced by co-trimoxazole 980 mg twice daily. In resistant cases rifampicin and sulfadoxine–pyrimethamine can be tried[48].

The results of medical treatment in patients with eumycetoma have not been encouraging. Griseofulvin 500 mg three times daily and penicillin 600 000–800 000 units daily have shown promising results when given for a long period, ranging from 1 to 10 years. Ketoconazole and itraconazole have been tried with some success[49]. However, these drugs are rather expensive and therefore not readily available in endemic areas[50]. Another disadvantage is that such drugs must be given for long periods (from 6 months to 10 years) to effect cure[45,49].

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Prevalence of abdominal aortic aneurysm in the offspring of patients dying from aneurysm rupture

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The prevalence of abdominal aortic aneurysm (AAA) is high in the brothers of patients with aneurysm. A genetic component in the development of AAA has, therefore, been postulated. In this study the offspring of patients who had died from AAA rupture were invited to undergo ultrasonography of the abdominal aorta. The attendance rate was 69 per cent. Thirty-nine sons of median age 60 (range 45–75) years and 23 daughters of median age 62 (range 42–80) years were examined. Abdominal aortic dilatation was found in eight men and one woman. The presence of aortic dilatation in these nine cases was not related to age, hypertension, smoking or symptoms of occlusive arterial disease. It is concluded that the sons of those who have died from ruptured AAA constitute a high-risk group for the development of this condition and should be considered for further screening.

Abdominal aortic aneurysm (AAA) is found predominantly among elderly men[1]. Most AAAs never rupture[1], but if this does occur the mortality rate without operation is 100 per cent and emergency surgery only marginally reduces this figure[2,3]. It is estimated that around 1 per cent of middle-aged to elderly men die from AAA[4,5]. The disease is often without symptoms until rupture, therefore to detect aortic dilatation at an asymptomatic stage would need some form of screening programme. To increase the efficiency of screening it is important to define groups at special risk. There are several such groups but the highest prevalence so far has been found in the brothers of patients with AAA[6–9]. There has been no study of the prevalence of aneurysm among the sons and daughters of patients with the condition. The reason for this may be that the offspring were not old enough to develop dilatation when AAA was diagnosed in the parent. There are genetic data indicating that at least some aneurysms are inherited, although the pattern of inheritance is complex[10,11]. The aim of this study was to analyse the prevalence of AAA among the sons and daughters of patients dying from ruptured aneurysm.

Patients and methods

A total of 155 patients with ruptured AAA who underwent either autopsy between 1958 and 1980 or forensic autopsy between 1970 and 1980 were registered for the study. The local parish administration of each patient was contacted and asked for information on the natural children of each. This process was often complicated because the proband had to be traced back to the parish where they had lived at the time of the birth of the child The latter then had to be traced to a present address A total of 90 offspring (53 men and 37 women) were identified living in proximity to Malmö These 90 people were informed about the investigation and invited to undergo a physical and ultrasonographic examination. Sixty-two (69 per cent) accepted the invitation: 39 men of median age 60 (range 42–75) years and 23 women of median age 62 (range 42–80) years In eight families more than one person agreed to the examination

Ultrasonography was performed using real-time equipment (3·5-MHz Acuson 128; Acuson, California, USA, or Hitachi EUB340; Hitachi, Tokyo, Japan). All examinations were performed by experienced radiologists with special training in ultrasonography. The abdominal aorta was examined throughout its length and the maximum external diameter perpendicular to the long axis registered. Dilatation was defined as a localized dilatation of the abdominal aorta or a maximum aortic diameter below the renal arteries exceeding 29 mm.

The 62 people undergoing examination were interviewed using a questionnaire about smoking habits, previous myocardial infarction, cerebrovascular lesions and vascular surgery, current antihypertensive drug therapy and diabetes mellitus The height, weight, blood pressure and ankle brachial pressure index were measured for all individuals.

The χ^2 test was used to assess differences in proportions between groups (using Yates' correction if $n < 5$) and the two-tailed Mann–Whitney *U* test for differences between ordinal data of groups. $P < 0·05$ was considered statistically significant

Results

Abdominal aortic dilatation was found in eight men and one woman. The frequency among the sons was 21 per cent (95 per cent confidence interval (c.i.) 8–33 per cent) and among the daughters 4 per cent (95 per cent c.i. 0–13 per cent). The maximum width of aortic dilatation was 17, 26, 28, 29, 37, 39, 45 and 68 mm in the eight men and 31 mm in the woman. The ages of the affected sons were 62, 59, 75, 53, 71, 73, 64 and 53 years respectively, and that of the daughter 68 years. The affected men did not differ in age from the men without aortic dilatation ($P = 0·13$). None of the affected people came from the same family and no dilatation was known before ultrasonography. None of the risk factors, i.e. smoking, previous myocardial infarction, cerebrovascular lesions and vascular surgery, treatment for hypertension or diabetes mellitus, showed significant difference in those who had aortic dilatation. All 62 individuals examined had an ankle:brachial pressure index $\geq 1·0$ Height, weight and blood pressure were not statistically related to the presence of aortic dilatation.

Discussion

Forensic autopsies were not included in the registry before 1970 but after this date the cases represent virtually all ruptured aneurysms in the community[12] The acceptance rate of investigation at 69 per cent was comparable to that in other screening studies of this type[7,13]. The men who attended for investigation were significantly older than those who did not ($P = 0·007$), among the women there was no difference in age ($P = 0·6$). As far as age is concerned there is an indication that the proportion with aortic dilatation in those who attended investigation may be higher than in those who did not.

Ultrasonography is a well established method of studying the abdominal aorta[14,15]. Although some investigators have described difficulties in establishing the exact aortic diameter[16,17], ultrasonography gives a good morphological image of this vessel. In all cases of dilatation in the present study there was a defined localized bulging of the aorta although in one patient this was of relatively small diameter

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Table 1 *Ultrasonographic screening studies of the prevalence of abdominal aortic aneurysm in siblings of patients with this condition*

		Men			Women		
Reference	Year	No studied	No. with AAA	Prevalence (%)	No. studied	No with AAA	Prevalence (%)
Bengtsson *et al.*[7]	1989	35	10	29 (14–44)	52	3	6 (0–12)
Collin and Walton[8]	1989	17	5	29 (8–51)	15	0	0
Webster *et al.*[9]	1991	24	5	21 (13–29)	30	2	7 (2–11)
Compilation		76	20	26 (15–36)	97	5	5 (1–10)

Values in parentheses are 95 per cent confidence intervals. AAA, abdominal aortic aneurysm

(17 mm) but in this instance the common iliac artery was also dilated bilaterally. While there is no consensus on the definition of AAA, because all aneurysms start from a normal aorta, we preferred to include all cases where the vessel was increased in size distal to the renal arteries. No instance of general dilatation of the aorta was found.

The prevalence of AAA in the population is highly age and sex dependent[1,18]. The definition of AAA is also of great importance with respect to the detected prevalence. The difficulty concerning definition is especially important when discussing small aneurysms. To be able to compare the prevalence of AAA in different studies these factors must be considered. The mean age of the men in the present study was 61 years, low compared with that used for prevalence studies of the normal population[19–21]. In a population study by Scott *et al.*[19] the prevalence was 7·9 per cent (95 per cent c.i. 6·7–9·1 per cent) in people of 60–80 years old, AAA being defined as an abdominal aortic diameter >30 mm. Using the same definition, the prevalence in the present study is 10 per cent (95 per cent c.i. 1–20 per cent). In a study by Collin *et al.*[20] of men aged 65–74 years, 5·4 per cent (95 per cent c.i. 3·3–7·5 per cent) had AAA, defined as $\geqslant 5$ mm expansion below the renal arteries compared with the suprarenal measurement. The corresponding figure in the present series is 18 per cent (95 per cent c.i. 8–28 per cent). O'Kelly and Heather[21], also investigating men aged 65–70 years and using a comparable definition to that in the present study, found 6·3 per cent (95 per cent c.i. 4·2–8·4 per cent) with AAA. Because there were relatively few individuals in the present study group, statistical comparison with the above findings was not considered meaningful.

A familial occurrence of AAA was first reported from Sweden[22] and the USA[23]. There are three systematic ultrasonographic screening studies of siblings of patients with AAA, all indicating 20–30 per cent prevalence among men (*Table 1*). The prevalence of AAA among sons in the present paper agrees with these sibling studies. No other systematic screening of sons and daughters of patients with AAA has yet been reported. The screening studies of siblings are still fairly small but brothers of patients with AAA certainly belong to a high-risk group.

In conclusion, sons of patients with ruptured AAA seem to have a high asymptomatic prevalence of the same condition. The result of the present study supports the hypothesis of a genetic component in the development of AAA. The mode of inheritance is under debate[10,24]. Sons of patients with ruptured aneurysm are an important group who are at risk of AAA and should be considered for screening.

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Case report

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False aneurysm of the abdominal aorta following pancreatectomy

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False aneurysms of the abdominal aorta are rare, usually follow trauma and often present years after the initial injury. Patients may be younger than the usual age for aortic aneurysms and the diagnosis is often overlooked, with an attendant risk of rupture. This paper describes a patient with a large false aneurysm that developed 10 years after distal pancreatectomy.

Case report

A 61-year-old man was referred with a spontaneous left calf deep vein thrombosis (DVT), which was confirmed by ascending venography. He was given anticoagulant therapy and underwent abdominal ultrasonography to exclude an occult malignancy The scan demonstrated a saccular aneurysm of the upper abdominal aorta 5 cm in diameter

The patient had undergone distal pancreatectomy 10 years earlier for chronic alcohol-related pancreatitis. He smoked 20 cigarettes a day but had no symptoms of cardiovascular disease, although he was aware of an uncomfortable 'lump' in the epigastrium The patient appeared healthy, was haemodynamically stable, and had a non-tender pulsatile mass in the epigastrium All peripheral pulses were normal, with some residual tenderness and swelling of the left calf following DVT Routine full blood count and biochemical findings were normal, as were the results of chest radiography

A mass of 8 cm arising from the aorta anterior to the pancreatic bed and left renal vein was seen on computed tomography (*Figure 1*) The appearance was of a pseudoaneurysm Angiography was performed to localize the origin from the aorta and to confirm that this was not an inflammatory mass adherent to the aorta

At operation a large false aneurysm arising from the front of the aorta below the level of the renal arteries was excised, and the resulting defect was repaired with a Dacron (Du Pont, Stevenage, UK) patch Following a spontaneous cerebrovascular accident on the fourth day after surgery, recovery was complete, and the patient remains asymptomatic 6 months after operation

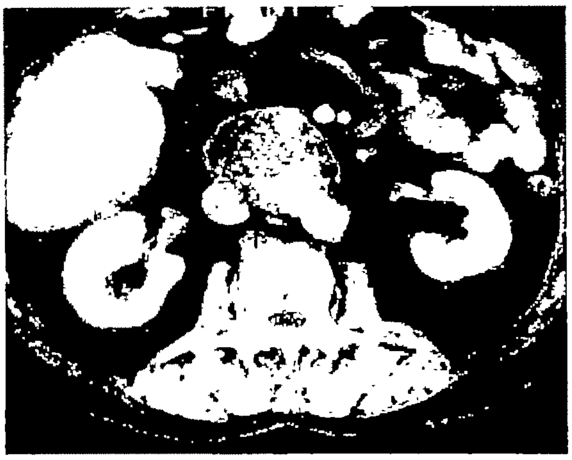

Figure 1 *Abdominal computed tomography demonstrating an anterior false aneurysm Note contrast within the aneurysmal lumen*

Discussion

The anterior aneurysm just below the renal vessels was probably caused by injury to the aorta during surgical dissection. The complication has not been reported previously, perhaps because most pancreatectomies are performed for malignancy in patients with poor life expectancy.

Pseudoaneurysm of the abdominal aorta is rare and has previously always followed some form of abdominal trauma, which may explain why patients have been exclusively male[1]. The usual sequel to aortic injury is full-thickness disruption and fatal haemorrhage, however, the aortic wall in the young is more resilient to blunt trauma, so that laceration of the intima and media may be contained by the adventitia and result in a false aneurysm. Most cases follow penetrating trauma, with only 25 per cent occurring after blunt injury Those following blunt trauma occur almost entirely in the distal aorta and at the aortic bifurcation[2]. The distribution of false aneurysms following penetrating trauma is more random, with the proximal abdominal aorta affected as often as the distal vessel[3]

The reported times to presentation range from 4 days to 27 years, but the majority present within 2 years of injury[2]. Most patients present with complications arising in the pseudoaneurysm, an abdominal mass associated with a bruit or symptoms of compression involving surrounding structures[1]. Aortocaval fistulation may occur in traumatic pseudoaneurysms[4]. Rupture does happen; six of 22 patients have died from this complication[1].

Most false aneurysms may be repaired with a simple patch, but occasionally suprarenal false aneurysms require extensive surgery, with reimplantation of the renal or visceral arteries.

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Aetiology and treatment of chylous ascites

A series of 45 patients with chylous ascites has been reviewed. The age at presentation ranged from 1 to 80 (median 12) years; 23 patients were aged ≤15 years. Thirty-five patients had an abnormality of the lymphatics (primary chylous ascites); in the remaining ten, the ascites was secondary to other conditions, principally non-Hodgkin's lymphoma (six patients). Two principal mechanisms of ascites formation were identified using lymphangiography and inspection at laparotomy: leakage from retroperitoneal megalymphatics, usually through a visible lymphoperitoneal fistula (14 patients); and leakage from dilated subserosal lymphatics of the small intestine, invariably associated with leaking lacteals causing protein-losing enteropathy (24 patients). Both sites of leakage were present in a further five patients. In the remaining two patients, chyle was leaking from normal mesenteric lymphatics, in one via a ruptured mesenteric lymph cyst and in the other from the site of a previous lymph node biopsy. Other associated lymphatic abnormalities were present in 36 patients, lymphoedema of the leg being the commonest (26 patients). All patients were initially treated conservatively with dietary manipulation; this was the most satisfactory treatment for those with leaking small bowel lymphatics. Surgery (fistula closure, bowel resection or insertion of a peritoneovenous shunt) was performed in 30 patients. Closure of a retroperitoneal fistula, when present, was the most successful operation, curing seven of the 12 patients so treated.

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In 1627, Asellius published the first accurate description of vessels in the mesentery of a dog containing a milky white fluid[1]. Chylous ascites (the collection of chyle within the peritoneal cavity) was first described in 1691 by Morton after performing paracentesis on an 18-month-old boy[2]. Trauma was recognized as a cause of chylous effusions by 17th-century physicians, but in 1705 Morton recognized the role of other disease processes[3]. In 1854 Virchow[4] described chylous ascites in a new born calf that had suffered a subclavian vein thrombosis. In recent years a number of small series of patients with chylous ascites have been reported[5–8], but with little consistency in proposed aetiology, diagnosis or treatment.

Because chylous ascites is both uncommon and sometimes subclinical, its prevalence and aetiology are hard to define. Although different pathological processes might be responsible, three principal mechanisms have been proposed[9]: (1) direct leakage of chyle through a lymphoperitoneal fistula, nearly always associated with abnormal retroperitoneal lymphatic vessels; (2) exudation of chyle through the walls of retroperitoneal megalymphatics without a visible fistula; and (3) exudation (or leakage following rupture) of chyle from dilated lymphatics on the wall of the bowel and in the mesentery, caused by obstruction of the lymphatics at the base of the mesentery or in the cisterna chyli and/or thoracic duct (Protein-losing enteropathy usually accompanies this condition.)

The aim of this study was to define the aetiology of chylous ascites and to correlate this with methods and outcome of treatment. The influence of protein-losing enteropathy on prognosis was also investigated.

Patients and methods

A total of 5000 patients with a final diagnosis of lymphatic disease referred to this department between 1953 and 1989 have been reviewed. Chylous ascites was identified in 54 patients (1·1 per cent). Nine have been excluded from this study because of inadequate documentation. The remaining 45 patients have been reviewed retrospectively. Their median age at presentation was 12 (range 1–80) years; 23 patients were aged ≤15 years. The male:female ratio was 1:3.1.

Clinical presentation and investigation

Thirty-four patients presented with abdominal distension, 27 with malnutrition and hypoproteinaemia, 21 with dyspnoea and 21 with steatorrhoea (*Table 1*). Three patients presented with acute abdominal pain, which was initially misinterpreted as acute appendicitis. Of the 45 patients with chylous ascites, a definite diagnosis of ascites was made without laparotomy in 40. Free peritoneal chyle was discovered incidentally at laparotomy in five. Bipedal lymphangiography was successfully performed in 42 patients. In two lymphangiography was unsuccessful and in one was omitted. Eight patients also underwent mesenteric lymphangiography[10–12] during laparotomy. Since the early 1970s, loss of protein from the bowel has been measured using the chromium chloride test[13,14]. This involves an intravenous injection of $^{51}CrCl_3$, which rapidly fixes to circulating plasma proteins. The amount of labelled protein appearing in the stools over the next 5 days is a measure of the degree of protein loss from the lacteals (normally <1·5 per cent). This test was performed on nine patients, of whom all but one had clinical evidence of protein-losing enteropathy.

Conservative treatment

After confirmation of the diagnosis, all patients were initially treated conservatively by dietary correction of any fluid, electrolyte, protein, calcium and vitamin D deficiencies, and a fat-free diet with the fat being replaced by medium-chain triglycerides. No patient received total parenteral nutrition. Gross abdominal distension caused by the ascites

Table 1 *Frequency of presenting symptoms in patients with chylous ascites*

Presenting symptom	Patients affected
Abdominal distension	34
Malnutrition/hypoproteinaemia	27
Dyspnoea	21
Steatorrhoea	21

Based on a presentation to The Association of Surgeons of Great Britain and Ireland in Oxford, UK, 3–5 April 1991

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was treated by paracentesis Radiotherapy and/or chemotherapy was employed when the chylous ascites was found to be secondary to malignant disease in the mesenteric or retroperitoneal lymph nodes

Surgical treatment

Laparotomy was performed when patients continued to lose weight or failed to grow, or if severe metabolic disturbances or gross ascites persisted Fistulas between the peritoneal cavity and retroperitoneal megalymphatics were closed by direct suture or ligation of the abnormal lymphatics When the mechanism of ascites formation was exudation from the bowel wall and mesentery, the most severely affected segment of small bowel was resected In a few patients in whom neither of these procedures was applicable, a LeVeen peritoneovenous shunt[15,16] was inserted Some patients have undergone multiple operations Dietary control was continued after operation for a variable period depending on the effect of surgery on the ascites

Assessment of results

The results of treatment were classified as follows

1. Cured complete resolution of ascites and cessation of protein-losing enteropathy (when present)
2. Improved. marked improvement in abdominal distension and quality of life, and reduction of protein-losing enteropathy (when present)
3. Poor result no change (or deterioration) in abdominal distension and/or quality of life and/or protein-losing enteropathy

Patients were followed up with regular clinical examinations in the outpatient clinic or by postal questionnaire where such visits were not possible

Results

Diagnostic investigation

Bipedal lymphangiography. Forty-two patients underwent successful bipedal ascending lymphangiography, which gave abnormal results in 40 (*Table 2*) One patient presented before the advent of bipedal lymphangiography and two patients in whom this technique failed had total distal lymphatic obliteration Twenty-five patients had abnormal retroperitoneal lymphatics, ten of whom had hypoplastic or aplastic lymphatics and 15 of whom had megalymphatics (*Figure 1a*); 17 patients had normal retroperitoneal lymphatics. Lymphangiography revealed the presence of a lymphoperitoneal fistula (*Figure 1b*) as the only cause of chylous ascites in 12 of the 14 patients with this abnormality Lymphangiography was unsuccessful in two of these 14 patients as discussed above. Ten of these patients had megalymphatics in the lumbar region, with the abnormality extending into the lower limbs in seven and/or the chest in three. Lymphatic obliteration or aplasia (*Figure 2a*) was seen in all patients with leaking small bowel lymphatics (who were identified at laparotomy, by mesenteric lymphangiography (*Figure 2b*), by the chromium chloride test or clinically), affecting the lower limb in 16 patients and the lumbar lymphatics in ten. A combination of a lymphoperitoneal fistula with leaking bowel and mesenteric lymphatics was identified at lymphangiography in all five affected patients. Lumbar megalymphatics were present in the five patients with combined fistula and leaking bowel. Chest megalymphatics were also present in two. One patient also had aplastic lymphatics of the lower limb

Laparotomy. Laparotomy was necessary to detect a fistula in two patients. It was also needed to detect leaking small bowel lymphatics in 23 of the 29 patients with this abnormality and to identify the two patients with mesenteric chyle leakage (one from a mesenteric cyst, one from a lymph node biopsy site)

Mesenteric lymphangiography In addition to bipedal lymphangiography, eight patients underwent mesenteric lymphangiography[12], which showed occlusion of the mesenteric lymphatics in six and of the thoracic duct in one. The patient with a leaking mesenteric cyst had normal mesenteric lymphatics. Mesenteric lymphangiography was not performed on the other patients with leaking bowel lymphatics because the abnormality was obvious and the state of the retroperitoneal lymphatics known from bipedal lymphangiography

Chromium chloride test. Of the nine patients thought to have protein-losing enteropathy in whom the chromium chloride test was performed, seven had an abnormal result (mean 14 *versus* normal <1·5 per cent) These patients all had leaking small bowel lymphatics, as determined at laparotomy. The test result was normal in two patients

Aetiology

Chylous ascites was associated with primary lymphatic disease (therefore classified as primary chylous ascites) in 35 patients, in seven of whom the abdominal distension was apparent at birth. In ten patients the ascites was secondary to other conditions (secondary chylous ascites), six of these had non-Hodgkin's lymphoma. Five of these six patients had leaking bowel and mesenteric lymphatics and the sixth had an iatrogenic fistula following a mesenteric lymph node biopsy performed 4 months earlier. The remaining four cases of secondary chylous ascites were caused by an abdominal stab wound, lymph node fibrosis following irradiation for a resected large bowel cancer, thoracic duct obstruction caused by correction of pulmonary artery stenosis, and bilateral subclavian vein thrombosis (one case of each). *Table 3* shows the relationship between aetiology and mechanism of chylous ascites. The overall mechanism of production of both primary and secondary ascites was lymphoperitoneal fistula in 14 patients (fistula group), mesenteric lymph node obstruction causing lacteal and serosal lymph exudation in 24 (leaking small bowel group), and a combination of both in five (combined group). In one patient the cause was a leaking solitary mesenteric cyst, in another a leak from the site of a surgical lymph node biopsy (miscellaneous group). All patients with obstructed lacteals and leaking subserosal lymphatics (primary or secondary) had clinical and biochemical evidence of protein-losing enteropathy. In nine patients this was confirmed by the chromium chloride test Adults were affected more frequently by protein-losing enteropathy than children, with 20 of 22 adult patients affected compared with nine of 23 children

Table 2 *Findings at lymphangiography in relation to the mechanism of chylous ascites in 42 patients*

	Lymphatic obliteration or aplasia		Megalymphatics		
Mechanism of chylous ascites	Lower limb	Iliac or lumbar	Lower limb	Lumbar	Chest
Lymphoperitoneal fistula (*n* = 12)	2	0	7	10	3
Leaking bowel (*n* = 23)	16	10	0	0	0
Combined fistula and leaking bowel (*n* = 5)	1	0	0	5	2
Miscellaneous (*n* = 2)	0	0	0	0	0
Total (*n* = 42)	19	10	7	15	5

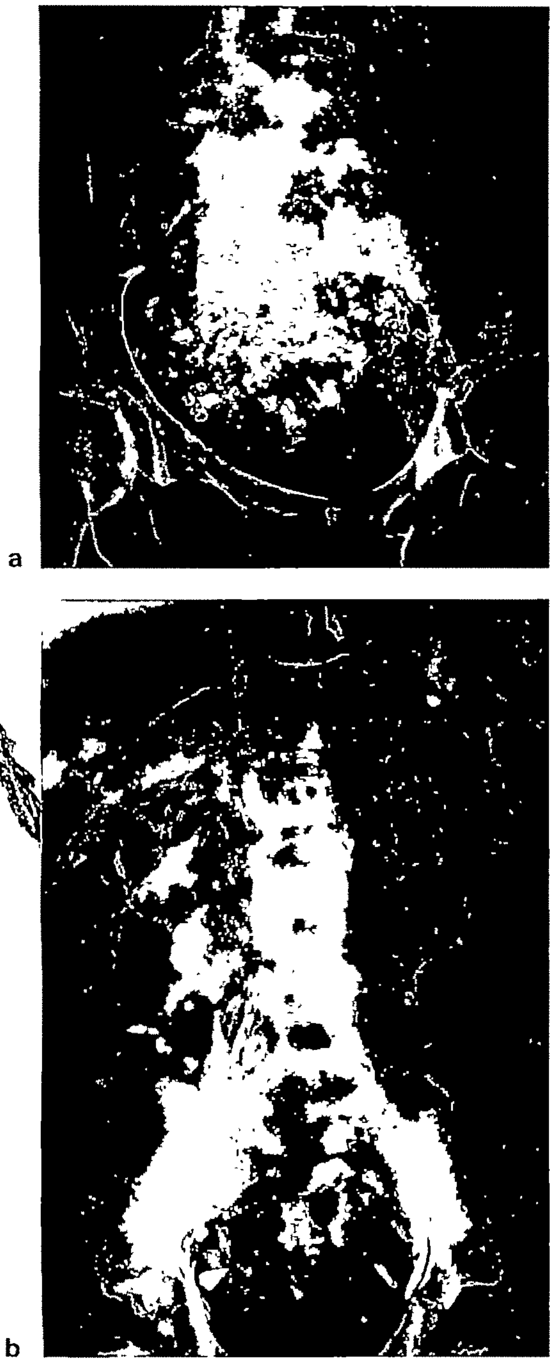

Figure 1 **a** *Lymphangiectasis (megalymphatics) of all the retroperitoneal lymphatics In this radiograph it is not possible to distinguish between intralymphatic Lipiodol (May and Baker, Dagenham, UK) and Lipiodol free in the peritoneal cavity This patient had multiple lymphoperitoneal fistulas* **b** *Radiograph showing lymphangiectasis of the lymphatics in the right para-aortic region This film was taken 24 h after the injection of Lipiodol and shows faint filling of the abnormal lymphatics, but large droplets of Lipiodol are free in the peritoneal cavity This patient had one large lymphoperitoneal fistula just below the foramen of Winslow*

Other lymphatic abnormalities

Other lymphatic abnormalities were present in 36 patients, including 29 of the 35 with primary chylous ascites and seven of the ten patients with secondary chylous ascites, all of whom had chylothorax Twenty-six patients had lymphoedema of the lower limb, present in 14 since birth. The leg lymphoedema preceded the chylous ascites by a mean of 11·6 years. The other associated lymphatic abnormalities, including chylothorax, chylopericardium, chylometrorrhoea, and genital, arm and facial lymphoedema, are summarized in *Table 4*

Conservative treatment

Table 5 shows the treatment of chylous ascites in relation to the mechanism Fifteen patients were treated with fluid, mineral and dietary manipulation alone Chemotherapy and radiotherapy were required for the six with lymphoma. The mean follow-up for this conservatively treated group was 77·2 (range 1–264) months One patient was cured and six were improved, but conservative treatment had no effect in eight patients.

Surgical treatment

Thirty patients were treated surgically (*Table 6*) Laparotomy was performed on 12 of the 14 thought to have a fistula; the

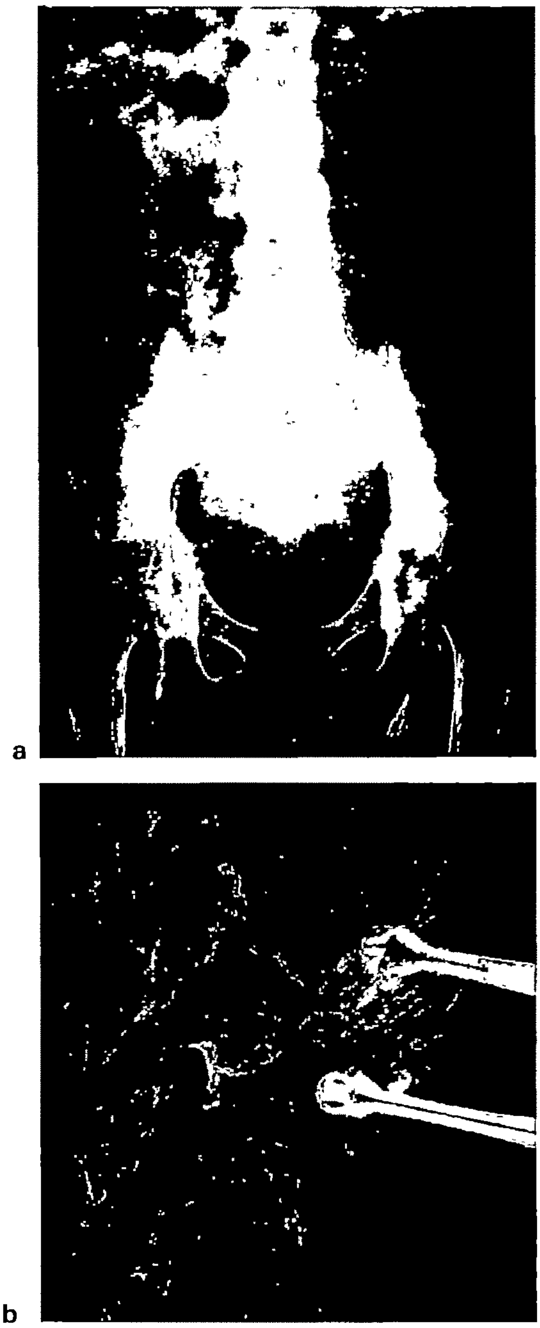

Figure 2 **a** *Lymphangiogram of a patient with chylous ascites and protein-losing enteropathy caused by leaking subserosal and submucosal lacteals, respectively, all are secondary to a primary mesenteric lymph node obstruction The lymphangiogram shows obliteration of the right iliac and right para-aortic lymphatics (aplasia)* **b** *Mesenteric lymphangiogram of the same patient showing an obstruction to flow into the cysterna chyli and retrograde flow into the lymphatics of the bowel wall Lipiodol injected into a normal lacteal flows directly into the cysterna chyli, never retrogradely into the bowel wall*

other two were not explored because their ascites was very mild. Closure of the fistula or excision of the leaking retroperitoneal lymphatics cured seven, and three were improved. Two patients were not helped. Laparotomy revealed leaking serosal lymphatics caused by primary mesenteric lymph node fibrosis in ten patients. All ten had resection of the abnormal or most diseased segment of bowel. One patient was cured, five improved and four had a poor result (mean follow-up 53·3 months). Another patient had a mesenteric cyst excised and was cured, and another who had a fistula at the site of a lymph node biopsy improved after resection of the leaking mesentery and a segment of small bowel. Nine patients had gross serosal leakage from the whole of their small bowel and a peritoneovenous shunt was therefore inserted. Within 3–6 months all nine shunts were blocked. Two of these patients later underwent bowel resection. A third subsequently underwent ligation of retroperitoneal megalymphatics that were undetected at the first laparotomy and was cured. *Table 7* shows the overall results of treatment.

There was one postoperative death: a 7-year-old boy with generalized lymphangiectasia (abdomen and chest) who presented with severe ascites and massive bilateral chylothorax died from sepsis and multisystem organ failure after the urgent insertion of a LeVeen shunt. One patient had a chest infection after operation.

Follow-up of the 30 patients treated surgically ranged between 1 month and 17 years (mean 50·3 months). Overall, ten patients were cured and 11 were improved. Of the nine patients with a poor result, seven died, four within 3 years of surgery. Treatment failure and/or death invariably occurred in patients with extensive whole-body abnormalities beyond surgical correction or repair, or involvement of the entire small bowel. During the period of follow-up (mean 61·3 (range 1–264) months), a total of 13 patients died. Seven of these were in the surgical group and six were treated conservatively. Ten of the 13 deaths occurred in the leaking small bowel group (four surgically treated and six medically). The mortality rate was higher in adults, especially in the presence of protein-losing enteropathy, but this was attributable to malignant disease. Twenty-one patients were cured or improved by surgery and seven by conservative treatment.

Discussion

The incidence of chylous ascites is unclear, but is probably between 1 : 50 000 and 1 : 100 000 hospital admissions[17], its rarity is reflected by the small numbers of patients reported in previous series[5–8,18–20]. The condition represents 1·1 per cent of all the lymphatic abnormalities seen by the authors in the past 25 years.

Chylous ascites may occur in response to various pathological processes. In 1910, Wallis *et al.*[21] concluded that no single aetiological factor prevailed. The condition has been reported in association with malignant abdominal neoplasms, infections (filariasis and tuberculosis), surgical and traumatic injuries of the abdominal lymphatic vessels, mesenteric adenitis, primary idiopathic pulmonary fibrosis, liver cirrhosis and congenital abnormalities of the lymphatic system[22–27]. However, it has been stated that the commonest aetiological factor in adults is abdominal malignancy[22,28], whereas congenital lymphatic abnormalities are more common in children[17]. In the adult patients in the present series, only six cases were secondary to malignancy, but there were no children with malignant disease. Primary chylous ascites accounted for 35 of the 45 patients and half of these were below the age of 15 years. However, this may simply reflect the pattern of referral. The association between chylous ascites and malignant disease is well known, as is the fact that the primary treatment is tackling the malignant disease. We suspect that these patients, who must be presenting throughout the country, are not referred whereas, because the diagnosis and treatment of primary chylous ascites is difficult, such patients are more likely to be referred to a centre interested in lymphatic disease.

Various classifications of chylous ascites have been proposed[5,9,17,28,29], some based on the physical appearance of the ascitic fluid (chylous, pseudochylous and chyliform)[22] or on its biochemical or bacteriological composition[18,29–31]. The appearance and composition of the chylous fluid are not, however, constant and depend on many factors, such as the size of the fat particles, cellular content and diet. An initial classification into primary and secondary conditions seems most satisfactory. That primary chylous ascites is often caused

Table 3 *Relationship between aetiology and causative mechanism of production of chylous ascites*

	Aetiology	
Mechanism of chylous ascites	Primary	Secondary
Lymphoperitoneal fistula ($n = 14$)	13	1
Leaking bowel ($n = 24$)	16 (16)	8 (8)
Combined fistula and leaking bowel ($n = 5$)	5 (5)	0
Miscellaneous ($n = 2$)	1	1
Total ($n = 45$)	35 (21)	10 (8)

Values in parentheses are numbers of patients with protein-losing enteropathy

Table 5 *Treatment of chylous ascites in relation to its causative mechanism*

		Surgical procedure		
Mechanism of chylous ascites	Diet alone	PVS	SBR	FCL
Lymphoperitoneal fistula ($n = 14$)	2	1	0	12
Leaking bowel ($n = 24$)	13	5	8	0
Combined fistula and leaking bowel ($n = 5$)	0	3	2	0
Miscellaneous ($n = 2$)	0	2	0	0
Total ($n = 45$)	15	11	10	12

PVS, peritoneovenous shunt, SBR, small bowel resection, FCL, fistula closure and/or ligation of lymphatics. Thirty-three surgical procedures were performed on 30 patients

Table 4 *Site of associated lymphatic abnormalities in 36 affected patients*

	Site of other lymphatic abnormalities						
Mechanism of chylous ascites	Leg	Arm	Face	Genitalia	Chylothorax	Chylopericardium	Chylometrorrhoea
Lymphoperitoneal fistula	9	1	0	2	2	0	1
Leaking bowel	16	5	1	8	8	1	0
Combined fistula and leaking bowel	1	0	1	0	2	1	0
Total	26	6	2	10	12	2	1

The abnormality in the leg, arm, face or genitalia was lymphoedema, nine other patients had no other detectable abnormalities

Table 6 *Results of surgical treatment*

Surgical procedure	No. of procedures	Cured	Improved	Poor result	Median follow-up (months)
Fistula closure	12	7	3	2	55·4
Small bowel resection	12	2	6	4	50·3
Peritoneovenous shunt	9	1	2	6	35·3
Total	33	10	11	12	

Thirty patients underwent 33 procedures

Table 7 *Relationship between causative mechanism of chylous ascites and results of treatment in 45 patients*

Mechanism of chylous ascites	Cured	Improved	Poor result*	Median follow-up (months)
Lymphoperitoneal fistula (*n* = 14)	7	3	4	56·9
Leaking bowel (*n* = 24)	2	12	10	72·3
Combined fistula and leaking bowel (*n* = 5)	1	3	1	20·6
Miscellaneous (*n* = 2)	1	1	0	18·5
Total (*n* = 45)	11	19	15	61·3

*Includes death

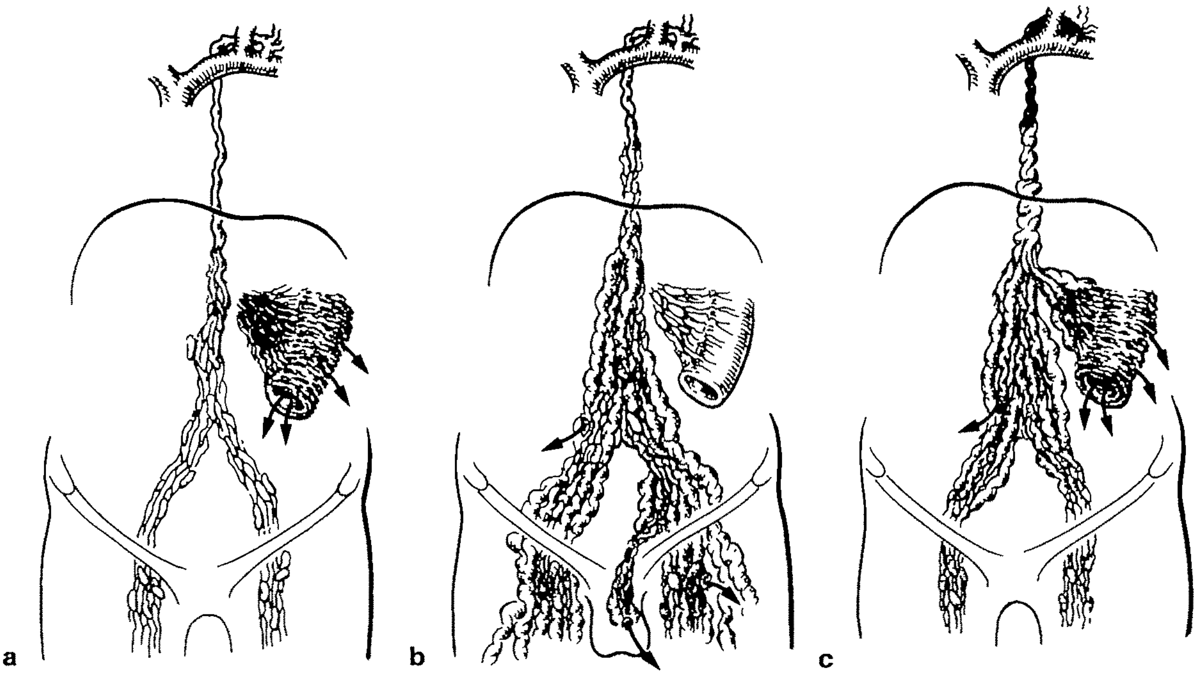

Figure 3 *The three common causes of chylous ascites.* **a** *Primary lymph node fibrosis (or infiltration by malignant disease) obstructing the flow of chyle from the bowel to the cysterna chyli This causes leakage of chyle from dilated subserosal lymphatics into the peritoneal cavity (chylous ascites), and the leakage of chyle back into the lumen of the bowel from dilated lacteals (protein-losing enteropathy) There is often iliac and inguinal lymph node and lymphatic obliteration.* **b** *Congenital retroperitoneal megalymphatics (lymphangiectasis) leaking through a fistula into the peritoneal cavity The bowel lymphatics are usually normal.* **c** *Dilated retroperitoneal megalymphatics, congenital as in* **b** *or secondary to a congenital or acquired thoracic duct obstruction, with a lymphoperitoneal fistula but also associated with dilated incompetent mesenteric lymphatics causing chyle leakage from subserosal lymphatics and leaking lacteals*

by a congenital abnormality is suggested by its frequent association with other lymphatic abnormalities, the commonest being lower limb lymphoedema (*Table 4*). Secondary chylous ascites is usually caused by malignancy, aortic surgery or penetrating abdominal trauma. The principal mechanisms of ascites formation are lymphoperitoneal fistula or leakage from the small bowel and mesenteric lymphatics, usually caused by obstruction in the mesenteric lymph nodes but sometimes by obstruction of the cysterna chyli or thoracic duct (*Figure 3*). Many patients present with abdominal distension but in this series 64 per cent presented with protein-losing enteropathy, having failed to notice their mild distension. The presence of enteropathy adversely affects prognosis because it indicates the possibility of an abnormality not amenable to surgical correction.

Chylous ascites is unusual in children under 15 years of age. Vasko and Tapper[17] reported only 59 of 140 cases (42 per cent), congenital abnormalities accounting for 23 of these Congenital abnormalities were present in 18 of 23 children in the present series under 15 years of age. Chylous ascites has been encountered in siblings[32], and a congenital hereditary form has been described in a colony of mice[33] Other less frequently associated conditions in children are trauma, tuberculosis, abdominal neoplasia and intestinal malrotation Press *et al.*[22] have recommended a conservative approach to children with chylous ascites and associated lymphatic abnormalities. We cannot support this view, particularly in the presence of lymphoperitoneal fistula. Chylous ascites is not a benign condition Mortality rates of 24 and 43 per cent have been reported in children and adults respectively[17]. In our experience, child and adult mortality rates are 8 and 50 per cent respectively.

The optimum management of patients with chylous ascites is unclear. In our experience, lymphangiography is the most important diagnostic and prognostic tool before performing exploratory laparotomy, but the chromium chloride test is useful for diagnosis and follow-up of patients with protein-losing enteropathy[13,14]. Lymphangiography usually defines any retroperitioneal lymphatic abnormality. Some authors[17,34] support immediate laparotomy, although others[6,22 35] have advocated an initial trial of conservative treatment, proceeding to surgery where this is unsuccessful In the light of the experience reported in the present series, the following approach is recommended.

1 When there is suspicion of protein-losing enteropathy, the diagnosis is confirmed by the chromium chloride test and the retroperitoneal lymphatics are normal, dietary manipulation and medical support are recommended as the initial treatment because the results of bowel resection are often disappointing. If conservative treatment fails, laparotomy should be performed and, if possible, the most affected part of the small bowel resected
2. When lymphangiography shows retroperitoneal megalymphatics and/or a lymphoperitoneal fistula and the chromium chloride test is normal, laparotomy with ligation of the affected lymphatics and fistula closure frequently results in cure
3 When lymphangiography shows abnormal retroperitoneal lymphatics but no fistula and the chromium chloride test is abnormal, dietary measures should be tried first, but if unsuccessful they should be followed by laparotomy so that the most affected segment of bowel can be resected and any retroperitioneal leakage controlled.

Patients with protein-losing enteropathy are a difficult group to treat; it is difficult to predict the extent of the bowel abnormality, and the results of both conservative and surgical treatment are often disappointing when the whole of the small bowel is involved The cause of the obstruction is undetermined. The lymph nodes at the base of the mesentery are swollen and full of chyle and yet do not allow the passage of chyle or, during lymphangiography, Lipiodol through them. This abnormality is often associated with both distal and proximal lymphatic obliteration, the latter is caused by lymph node fibrosis[36]. It is not unreasonable to suspect that a similar obstructing fibrosis has occurred in the most upstream mesenteric nodes. If this is the case, the only curative treatment would be a lymphatic bypass of the fibrosed nodes from either lacteals or distended nodes in the mesentery to the para-aortic nodes, if they are normal. The feasibility of such an operation is currently being investigated in an animal model. Another alternative would be a reversed enteromesenteric bridge to produce anastomoses between submucosal lymphatics and para-aortic lymph nodes, although it is unlikely that draining the chyle from a small segment of bowel would be adequate.

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Prostacyclin production from seeded prosthetic vascular grafts

Endothelial cell seeding has been proposed as a method of improving patency rates in small-calibre prosthetic vascular grafts. In vivo, *endothelial cells normally produce prostacyclin (PGI_2), a potent antiplatelet agent. The aim of this study was to determine whether seeded grafts show significant PGI_2 production after* in vivo *implantation. Grafts were seeded with either autologous canine venous endothelial cells or autologous microvascular endothelial cells. After 12 weeks, PGI_2 production was assessed under basal and stimulated conditions. Seeded grafts were compared with non-seeded controls and the corresponding aorta. The overall patency rate in seeded grafts was 80 per cent compared with 10 per cent in non-seeded grafts* ($P<0{\cdot}01$)*. Grafts seeded with cells from either source produced significantly more PGI_2 than unseeded grafts in both basal and stimulated states* ($P<0{\cdot}05$)*. The aorta produced significantly more PGI_2 than seeded grafts under both conditions* ($P<0{\cdot}01$)*. Endothelial cell seeding produces a functional graft and leads to an improved patency rate.*

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Endothelial cells produce a number of substances with either thrombotic or antithrombotic activity; the balance *in vivo* is normally in favour of the antithrombotic properties. This activity is brought about by a number of mechanisms, but one that is thought to be particularly important is the production of prostacyclin ($\mathrm{PGI_2}$)[1]. This potent inhibitor of platelet aggregation is released by normal endothelial cells in varying quantities depending on the vascular bed in question. It has previously been shown that endothelial cell seeding, using a preformed confluent layer of endothelial cells on prosthetic grafts, reduces graft thrombogenicity and improves patency rate[2]. The present study was designed to investigate the functional properties of grafts seeded with either autologous venous endothelial or microvascular endothelial cells.

Materials and methods

Ten conditioned Beagle dogs weighing 8–14 kg were used for graft implantation. Anaesthesia was carried out using sodium thiopentone (0·5–1 mg/kg) for induction, followed by maintenance with a combination of halothane (1·5–2 per cent), oxygen and nitrous oxide. Grafts in five dogs were seeded with autologous venous endothelial cells and in the other five with microvascular endothelial cells obtained from omentum.

Harvesting venous endothelial cells

Endothelial cells were harvested from the right external jugular vein of each animal. All side branches were tied while the vein was still *in situ* and the main length of vein handled as little as possible. The length of vein removed was about 10 cm from each dog. The harvested vessel was placed in ice-cold minimum essential medium (MEM) (Flow Laboratories, Irvine, UK). The harvested vein was cannulated and then distended with about 2 ml 0·1 per cent collagenase (Worthington CLS I, New Jersey, USA) at 37°C. It was then incubated at 37°C for 15 min. The cell suspension obtained after flushing the vein was spun at 200g for 7 min at 4°C and the cell pellet resuspended in 4 ml complete medium comprising medium M199, 20 per cent fetal calf serum (FCS), 100 units/ml penicillin, 100 μg/ml streptomycin, 20 mmol/l Hepes buffer, 2 mmol/l glutamine, 1 mmol/l pyruvate (all Flow Laboratories), 20 μg/ml endothelial cell growth supplement and 90 μg/ml heparin (Sigma Chemicals, Poole, UK). Cells were then plated into a 25-cm^2 tissue culture flask and grown for 7 days.

Harvesting microvascular endothelial cells

Endothelial cells were obtained from pieces of omentum. A small midline abdominal incision was made under general anaesthesia using sterile operating conditions. The omentum was delivered through the incision and a piece estimated to be about 10 g in weight excised. The incision was closed and the animal allowed to recover. The excised omentum was placed in ice-cold MEM until further processed.

A modification of the method of Kern *et al.*[3] was used to harvest cells. The omentum was processed within 1 h of harvesting and all procedures carried out under sterile conditions. The first step in the processing was introduced as an addition to Kern's method to remove as many mesothelial cells as possible before definitive endothelial cell harvest. This entailed incubating the intact specimen of omentum in 10 ml 0·1 per cent collagenase at 37°C for 20 min. After this preliminary incubation, the omentum was washed four times in MEM and then minced finely using two scalpel blades. The minced tissue was divided into four equal aliquots, each of which was placed in a 20-ml universal container (Sterilin; Corning, Stone, UK) containing 7 ml 0·1 per cent collagenase prewarmed to 37°C. The collagenase solution for this digestion was made up in MEM with 3 mmol/l glucose and 4 per cent bovine serum albumin (BSA) (APP, Brierley Hill, UK). The tubes were then incubated at 37°C on a roller-table rotating at 30 rev/min. After 15 min, the tubes were vigorously shaken and the resultant suspension from all four tubes passed through a 250-μm pore nylon mesh (Lockertex, Warrington, UK) to separate the undigested pieces. The tubes were then washed out with MEM containing 10 per cent FCS and this was also passed through the mesh. The filtrate was collected and centrifuged at 300g for 7 min; the supernatant was then removed and the cell pellet resuspended in 3 ml MEM with 10 per cent FCS. This cell suspension was subsequently filtered through 30-μm pore size nylon mesh (Lockertex). Clumps of endothelial cells were retained on the mesh and recovered by cutting out the mesh, transferring it to a centrifuge tube containing 20 ml MEM, and shaking it to dislodge the cells. The resulting suspension was centrifuged at 300g for 7 min and the cell pellet resuspended in 5 ml medium M199 with 20 per cent FCS. This suspension was then layered on to 15 ml BSA (5 per cent in medium M199). After 10 min at room temperature, the upper 5 ml of the gradient, which should contain any contaminating isolated stromal cells, was discarded. The remainder of the gradient was centrifuged at 300g for 7 min and the cell pellet finally resuspended in 4 ml complete medium. The cells were then plated into a 25-cm^2 tissue culture flask and grown for 7 days.

Seeding of grafts

After 7 days in tissue culture, the cells were used to seed polytetrafluoroethylene (PTFE) grafts. A 15-cm length of PTFE graft 4 mm in internal diameter (a gift from W. L. Gore, Woking, UK) was first secured in place inside a seeding chamber as previously described[2]

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The chamber with the graft *in situ* was sterilized and the luminal surface of the graft then coated with a 20-μg/ml fibronectin solution (Sigma).

Endothelial cells were released from the tissue culture flask with trypsin and resuspended in 8 ml complete medium. A cell count was made at this point using a haemocytometer. Cells were introduced into the graft in aliquots of 2 ml at 20-min intervals and with 90° rotation of the graft between each stage. The final aliquot was left inside the graft. The chamber was then placed on a roller-table rotating at 10 rev/h inside an incubator at 37°C. After incubation overnight, the graft was ready for implantation.

Graft implantation

Grafts were placed in the femoral region. Each animal received a graft seeded with its own endothelial cells and a contralateral non-seeded control graft. Each dog therefore acted as its own control. The profunda femoris artery was tied in continuity. Just before occlusion of the femoral vessel, the dog was given 100 units/kg heparin. Once occluded, an 8-cm length of the superficial femoral artery was excised. The grafts were then used to bridge the defect caused by this excision. The control graft consisted of an 8-cm length of plain PTFE cut from the same length of graft as that used for seeding. The unused portion of the seeded graft was stained with toluidine blue to assess the degree of cell coverage at implantation. Grafts were anastomosed end to end using 7/0 polypropylene sutures.

Removal of grafts

Grafts were left *in situ* for 12 weeks. The inguinal incisions were then reopened and the grafts dissected away from the surrounding tissue. After the skin incisions had been made, 100 units/kg heparin was given to prevent graft thrombosis during removal. A small length of aorta was also removed.

Prostacyclin release from grafts

Two segments from the middle third of each graft were taken after harvesting. Any adherent thrombus was gently washed from the graft surface. This was easily accomplished and it was not felt that carrying out such a procedure significantly altered the assay for PGI$_2$, even in grafts that occluded. The graft segments were placed in cold MEM and processed within 1 h. Two segments of the corresponding abdominal aorta were also placed in MEM. To obtain similar-sized specimens to compare PGI$_2$ release, 5-mm circular punch biopsies were taken from each segment using a cork borer. Each of these was placed in a single well of a 24-well plate (Nunc, Corning) with its luminal surface uppermost. Similar-sized biopsies of plain PTFE that had not been implanted were used as negative controls. The specimens were then covered with 1 ml plain MEM at 37°C. This was left for 5 min and then replaced with a further 1 ml MEM at 37°C. The plate was incubated at 37°C for 5 min and a 100-μl sample of the supernatant then taken from each well. This first sample represented the baseline PGI$_2$ level, the plate was then returned to the incubator for a further 25 min and then a second 100-μl sample taken. This aliquot represented the basal release of PGI$_2$. After this sample had been taken, 300 μl of a 2 units/ml thrombin solution (obtained from Sigma and made up in plain MEM) was added to each well. Thrombin was used to stimulate any endothelial cells present to release PGI$_2$ maximally. The plates were returned to the incubator and left for a further 10 min. At the end of this incubation, a further 100-μl sample was taken from each well. This aliquot represented the stimulated release of PGI$_2$. All the samples were frozen and stored at −70°C until further measurements were carried out. The measurement of PGI$_2$ levels was carried out using a TRK 790 radioimmunoassay kit (Amersham International, Amersham, UK).

Preparation of segments for light microscopy

The segments of the graft and corresponding artery were initially placed in formal saline. Further processing involved dehydration through graded alcohol, transfer to xylene for 180 min and then immobilization in wax over 4 h. The specimens were subsequently sectioned to 4 μm thickness on a base sledge microtome and stained with haematoxylin and eosin.

Statistical analysis

Results are given as mean(s.e.m.) unless otherwise stated. Comparisons of PGI$_2$ production between groups were made using Student's *t* test. Patency rate results were assessed by Fisher's exact test.

Results

A mean of $1{\cdot}4 \times 10^6$ venous endothelial cells were used to seed the grafts, the corresponding figure for microvascular cells was 2×10^6. All grafts showed a confluent lining of endothelial cells when the excess was stained with toluidine blue at the time of implantation.

Patency

In both groups, four of the five seeded grafts were patent at 12 weeks. In contrast, only one of the ten non-seeded grafts remained patent and this was in the microvascular group (overall $P<0{\cdot}01$ for seeded *versus* control grafts). The grafts were monitored daily with a hand-held Doppler ultrasonographic probe to determine patency; the grafts that occluded did so between 4 and 10 weeks.

Prostacyclin release

The negative control grafts (i.e. PTFE that had not been implanted) produced no detectable PGI$_2$ at any stage. The remainder of the results are shown in *Table 1*. The one unseeded graft that remained patent produced PGI$_2$ levels of 0·6 and 5·4 pg/min respectively for basal and stimulated conditions, i.e. similar values to those obtained with unseeded grafts that occluded. The seeded grafts that occluded produced only low levels of PGI$_2$, even when stimulated. The aorta consistently produced more PGI$_2$ than other preparations ($P<0{\cdot}01$) in basal and stimulated environments. There was no significant difference between basal release of PGI$_2$ from venous or microvascular endothelial cells. When stimulated, however, venous endothelial cells produced more PGI$_2$ than did microvascular cells ($P<0{\cdot}05$).

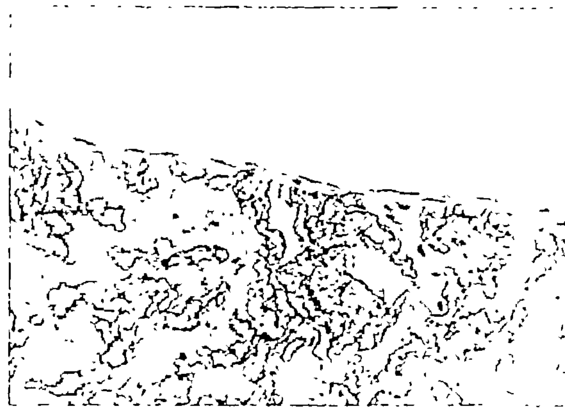

Figure 1 *Light microscopy of one of the seeded grafts on removal at 12 weeks showing a confluent monolayer of endothelial cells directly applied to the mid-portion of the graft. (Original magnification ×20)*

Table 1 *Release of prostacyclin from 5-mm punch biopsies of each graft*

	Prostacyclin (pg/min)			
	Aorta	Unseeded	Venous	Microvascular
Basal	123(15)*	1·6(0·9)	25·3(5·4)†	34·8(6·2)*
Stimulated	642(51)*	7·3(2·3)	303(55)†	94(27)†

Values are mean(s.e.m.). *$P<0{\cdot}01$, †$P<0{\cdot}05$ (*versus* unseeded grafts, Student's *t* test)

Graft histology

The eight seeded grafts that remained patent exhibited a clear layer of endothelial cells along their length (*Figure 1*). Endothelial cells could be seen forming a single monolayer with tight cell-to-cell contact. The two seeded grafts that occluded showed no obvious evidence of endothelial cells on the graft luminal surface. This was similar to the non-seeded grafts, even in the graft that remained patent.

Discussion

Autogenous saphenous vein is generally regarded as the best material for infrainguinal bypass, especially when the distal anastomosis is below the knee[4]. In some patients such vein is not available and prosthetic materials must be used. In an effort to improve the patency rate of these prosthetic materials, endothelial cell seeding has been proposed.

Vascular endothelium is a structurally simple but functionally complex tissue, the integrity of which is essential for normal vascular function The importance of the endothelium in maintaining normal blood fluidity was appreciated as long ago as 1856 by Virchow[5] and formed part of his classic triad of factors predisposing to thrombosis. The endothelium has central roles, not only in the maintenance of vascular tone and permeability, but also in the regulation of leucocyte traffic and the modulation of haemostasis and thrombosis. In the context of seeding synthetic grafts with endothelial cells, the ability of the resulting monolayer to function appropriately, particularly with regard to haemocompatibility, is paramount With this in mind, this study was carried out to investigate the functional nature of seeded grafts with respect to PGI_2 production.

Other studies confirm the present results in terms of the improved patency rate of small-calibre prosthetic grafts seeded with endothelial cells[6–10]. There are a number of reasons why this may occur. One of the main theoretical advantages of endothelial cell seeding is that such cells produce PGI_2 This, in turn, should lead to a reduced graft–platelet interaction. The present study has shown that this does indeed occur in an animal model. Seeded grafts produced significantly more PGI_2 at 12 weeks than controls in both basal and stimulated states Seeded grafts did not, however, produce the same quantities as the native artery. Sharp *et al.*[11] also showed that seeded grafts produce significant amounts of PGI_2 compared with controls. They used Dacron (Du Pont, Stevenage, UK) grafts and the relatively high level of production by their non-seeded controls was of note Clagett *et al.*[12] found a similar pattern using seeded Dacron grafts. In marked contrast, Sicard *et al* [13] found that non-seeded grafts produced significantly more PGI_2 than seeded grafts. This is difficult to explain unless the PGI_2 produced from the seeded grafts was derived from segments that had few, or even no, endothelial cells. Schmidt *et al.*[14] again showed significant PGI_2 production by seeded Dacron and, furthermore, that this was depressed by various antiplatelet preparations. To observe the effect of the new seeding procedure alone, the present study did not use any antiplatelet medication. Introducing this additional therapy might even have proven detrimental, because it would not only have inhibited thromboxane release from platelets, but would also have blocked the release of the PGI_2 from the endothelial cells[11]. No studies to date have given details on PGI_2 production from seeded PTFE grafts. The present results suggest that PGI_2 production from unseeded control grafts is very small, which contrasts with the Dacron studies. This may reflect the relative porosities of the two graft types. Capillary ingrowth into Dacron is much more pronounced than with PTFE and these vessels may contribute significantly to the PGI_2 levels measured from graft segments. The levels produced by the seeded PTFE are comparable to those obtained in most of the seeded Dacron studies. It is also worth noting that Bull *et al.*[15] have shown that mesothelial cell seeding of Dacron prostheses also leads to significant PGI_2 release compared with non-seeded controls.

The production of PGI_2 by endothelial cells acts to reduce platelet adhesion to the graft. This is important, because platelet adhesion is one of the initiating steps in graft occlusion. It has been shown that by implanting fully endothelialized grafts, even after 1 week, there is a significant reduction in platelet accumulation on the seeded surface[2]. Microvascular endothelial cells appear to produce similar amounts of PGI_2 in their basal state but significantly less than venous endothelial cells when stimulated with thrombin. This finding is similar to results obtained *in vitro* by Carter *et al* [16], where thrombin stimulated large-vessel PGI_2 production but not that of microvascular endothelial cells

In conclusion, this study has shown not only that endothelial cell seeding improves small-calibre prosthetic graft patency rates, but also that it leads to formation of a functional lining on the luminal surface of the graft. Seeding with either venous or microvascular endothelial cells appears to be equally effective.

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Serotonin-induced contractility in human saphenous vein is inhibited by naftidrofuryl

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Vascular endothelial denudation contributes to vasospasm by causing platelet aggregation and the subsequent release of vasoconstrictors such as serotonin. It has recently been suggested that naftidrofuryl fumarate (NFT) may oppose serotonin-induced vasoconstriction. Fourteen rings of human saphenous vein from 14 patients undergoing varicose vein surgery were tested in standard organ bath experiments. Cumulative dose–response curves and maximal contraction in response to serotonin were recorded and this was repeated in the presence of NFT at 10^{-6} *and* 10^{-3} *mol/l. The difference in maximal contractility between the three sets of curves was significant* ($P < 0{\cdot}0001$)*. Sensitivity to serotonin in each of the three curves was measured using the concentration for half-maximal response; differences were again significant* ($P < 0{\cdot}0001$)*. It is concluded that NFT reduces serotonin-induced contractility in a dose-dependent fashion in rings of human saphenous vein* in vitro*. These results suggest a possible role for NFT in reducing vasospasm and support further investigation of this drug.*

Serotonin has long been recognized as an important vasoconstrictor[1,2]. It is stored in granules within circulating platelets. When these aggregate in response to endothelial trauma, the granules are discharged and the stored serotonin released. It is suggested that the released serotonin acts directly on 5-HT_2 receptors within smooth muscle cells in the vessel wall to induce vasoconstriction[3,4]. This vasoconstriction may be of clinical significance and has been implicated in the pathogenesis of both coronary and peripheral vein bypass graft spasm[5,6].

Naftidrofuryl fumarate (NFT) (Praxilene; Lipha Pharmaceuticals, West Drayton, UK) has been used to treat intermittent claudication because of its supposed ability to increase the efficiency of cellular metabolism in ischaemic tissue[7–10]. However, recent animal studies have also shown that NFT is a specific 5-HT_2 receptor antagonist and inhibits serotonin-induced vasoconstriction[4,11,12]. The present study was therefore designed to assess the ability of NFT to antagonize serotonin-induced contraction in human vessels *in vitro*.

Materials and methods

Studies were performed on human saphenous vein *in vitro*. The proximal segment of long saphenous vein was excised with minimum trauma from patients undergoing varicose vein surgery and placed immediately in Krebs' solution (122 mmol l^{-1} NaCl, 4·4 mmol l^{-1} KCl, 1·2 mmol l^{-1} $MgCl_2$, 2·5 mmol l^{-1} $CaCl_2$, 15·4 mmol l^{-1} $NaHCO_3$, 1·2 mmol l^{-1} KH_2PO_4, 5·5 mmol l^{-1} dextrose) at 37°C. Veins were then cleared of adherent connective tissue and cut into rings of 4–5 mm in width. The rings were suspended in a conventional organ bath and connected to a force–displacement transducer linked to an isolated multichannel polygraph. The organ bath contained Krebs' solution at pH 7·4. The solution in the bath was changed every 15 min and continuously bubbled with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. The temperature of the bath was maintained at 37°C.

Drugs

NFT was dissolved in distilled water and tested for antiserotonin activity at two concentrations: 10^{-6} and 10^{-3} mol/l. Serotonin (5-hydroxytryptamine creatinine sulphate complex, Sigma Chemicals, St Louis, Missouri, USA) was dissolved in normal saline.

Rings were allowed to equilibrate at a constant tension of 1·5 g for 1 h. An optimal length–tension relationship for maximal contractility was established using 40 mmol/l KCl (in addition to the K^+ and Cl^- in the Krebs' solution).

The rings were then washed and equilibrated, and cumulative dose–response curves for serotonin recorded as a control (experiment 1). After recording the first curve, the rings were washed and re-equilibrated for 45 min, and the reproducibility of the contractile response confirmed using a submaximal dose of serotonin (5×10^{-5} mol/l). The rings were then incubated in 10^{-6} mol/l NFT for 30 min and a second dose–response curve recorded (experiment 2). The rings were again washed and allowed to equilibrate for 45 min, and the effective removal of the antagonist confirmed using the same submaximal dose of serotonin as before. Rings that retained the original responsiveness to serotonin were then incubated in 10^{-3} mol/l NFT for 30 min and a third dose–response curve to serotonin recorded (experiment 3). Reversibility of the antagonism by washing was again confirmed using the submaximal dose of serotonin. Only rings that remained responsive to serotonin throughout were included in the study. These rings were sent for histological examination to confirm the presence of endothelium.

Statistical analysis

Dose–response curves for each individual ring were analysed by probit analysis (SAS; SAS Institute, Cary, North Carolina, USA). The concentration at which 50 per cent of the maximal response for each ring was elicited (ED_{50}) was calculated for each curve separately. Maximal contractility was measured directly from the recorded dose–response curves and is expressed as tension in grams. All data are given as mean(s.e.m.). Differences in ED_{50} and maximal contractility were analysed using Student's paired *t* test.

Results from dose–response curves obtained after incubation with NFT (experiments 2 and 3) are expressed as percentages of the maximum contraction of the control curve (experiment 1).

Results

Histological examination confirmed the presence of endothelium in each of the vein rings used. Of the 31 rings initially tested, only 14 were used for the complete experiment. The remaining 17 were excluded because they failed to respond to serotonin initially ($n = 6$) or because the amplitude of the contraction elicited by the submaximal dose of serotonin progressively diminished during the experiment ($n = 11$).

Table 1 shows the maximal contractility for each of the three sets of curves ($n = 14$). In the control curves, mean(s.e.m.) maximal contractility was 62·1(4·1) g, whereas after preincuba-

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Table 1 *Response of human saphenous vein to serotonin alone and in the presence of naftidrofuryl*

	Maximal contractility (g)	ED_{50} (mol/l serotonin)
Serotonin	62·1(4·1)	$2·3(0·3) \times 10^{-7}$
Serotonin plus 10^{-6} mol/l NFT	20·9(1·4)	$8·7(1·0) \times 10^{-5}$
Serotonin plus 10^{-3} mol/l NFT	6·1(0·8)	$1·7(0·6) \times 10^{-4}$

Values are mean(s.e.m.). NFT, naftidrofuryl; ED_{50}, concentration for half-maximal response. $P < 0·0001$ between all groups (Student's *t* test)

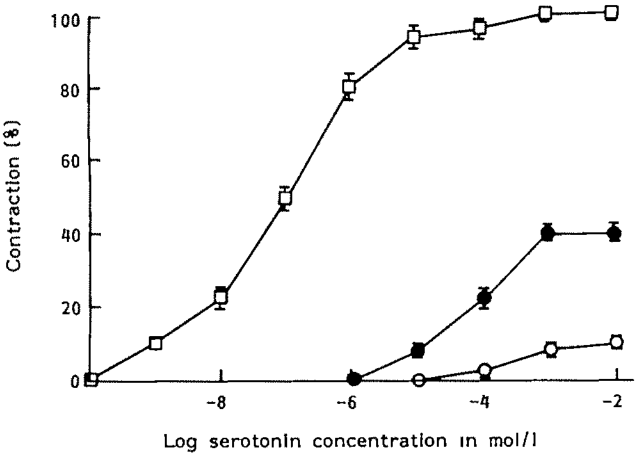

Figure 1 *Effects of increasing concentrations of naftidrofuryl (●, 10^{-6} mol/l, ○, 10^{-3} mol/l) on dose–response curves of human saphenous vein contracted by serotonin. Values are mean(s.e.m.) percentage of maximum contraction of the control curve* (□)

tion with 10^{-6} and 10^{-3} mol/l NFT it was 20·9(1·4) and 6·1(0·8) g respectively. The differences between any two groups were highly significant ($P < 0·0001$).

Standardized dose–response curves (*Figure 1*) showed a rightward shift with increase in concentration of NFT, suggesting a progressive decrease in sensitivity to serotonin with the increase in concentration of NFT in the bathing solution. The pattern of these plots, with suppression of the maximum response and a non-parallel shift of the second and third sets of curves, is suggestive of non-competitive antagonism.

The mean(s.e.m.) ED_{50} for serotonin increased progressively with addition of NFT (*Table 1*). It was $2·3(0·3) \times 10^{-7}$ mol/l for the control, increasing to $8·7(1·0) \times 10^{-5}$ mol/l for the lower and $1·7(0·6) \times 10^{-4}$ mol/l for the higher concentration of NFT. The differences between any two groups were again significant ($P < 0·0001$).

Discussion

This *in vitro* study demonstrates that NFT antagonizes serotonin-induced contraction of human saphenous vein in a dose-dependent and non-competitive manner. The maximal contractility of control rings was significantly reduced after preincubation with NFT, showing a reduction of more than 60 per cent with the physiological concentration[13] of 10^{-6} mol/l. However, the contractile response could not be completely abolished, even with the higher non-physiological concentration of NFT (10^{-3} mol/l) used in this study. Similar incomplete inhibition has been observed in animal experiments and is attributed to the intrinsic contractile activity of NFT[1,4]. This drug also blocks endogenous serotonin activity, as demonstrated by exposing the vessel preparation *in vitro* to human platelet-rich plasma[14].

NFT has been used for many years in patients with intermittent claudication. It is claimed to improve the efficiency of the Krebs cycle in ischaemic tissues by increasing oxygen uptake, improving glucose metabolism, increasing adenosine 5′-triphosphate production and lowering the lactate:pyruvate ratio[7–10]. The results from the present study support the growing evidence that NFT has antiserotonergic activity in humans and may have a clinical role in reducing serotonin-induced vasoconstriction.

In recent years, platelet-derived serotonin has been proposed as a major contributor in the pathogenesis of vasospasm. The vascular response to serotonin released from platelets will depend on the integrity of the endothelial cells, as they are responsible for its uptake and degradation[4]. Serotonin reaching 5-HT_1 receptors on the endothelial cells triggers the release of endothelium-derived relaxing factor (EDRF). However, if the endothelium is traumatized, this factor is not produced and platelet-derived serotonin induces vasoconstriction via the 5-HT_2 receptors on smooth muscle cells. Furthermore, the absence of endothelium allows platelet aggregation to persist[4,15–17]. Although the endothelium regenerates, it loses its ability to release EDRF[4]. The loss of this response favours abnormal vasoconstriction or spasm and platelet aggregation with release of platelet-derived growth factor, thus setting the stage for atherosclerosis and thrombosis[4,18,19].

It is of interest that atherosclerotic human vessels have increased sensitivity to serotonin[20], but it would be unwise to extrapolate the results of the present study to human arterial tissue. Nevertheless, NFT may have a valuable clinical role in reducing serotonin-induced vasospasm, particularly after intravascular manipulation such as angioplasty or vein bypass surgery.

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Case report

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Localized amyloid of the glans penis

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Case report

A 32-year-old caucasian man presented with an 8-week history of a painless mass (3 × 1 cm in size) on the glans penis. There were no urinary symptoms, and no past history of penile ulcers or trauma The mass was neither tender nor ulcerated and did not extend into the urethra or over the shaft of the penis There was no regional lymphadenopathy and general examination was unremarkable.

Excision biopsy was carried out Light and electron microscopy confirmed the presence of large amounts of diffuse subcutaneous amyloid (*Figure 1*) Congo red staining and birefringence was abolished by prior treatment of sections with potassium permanganate, showing the material to be AA amyloid, the type usually associated with chronic inflammatory conditions. There was no histological evidence of epithelial dysplasia

The patient's white cell count and differential count were normal, the erythrocyte sedimentation rate was 1 mm/h. Serum urea, creatinine and electrolyte levels, and results of liver function tests and electrophoresis, were all normal Further investigations, including rectal biopsy, did not show any evidence of systemic amyloidosis Findings at intravenous urography and cystoscopy were normal

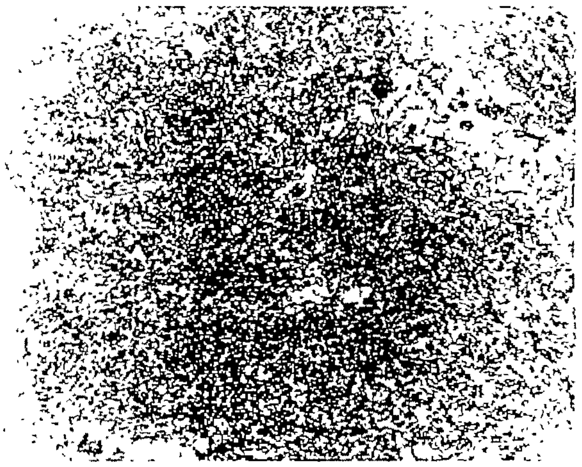

Figure 1 *Transmission electron micrograph showing numerous delicate fibrils, the classical appearance of amyloid (Original magnification ×5800)*

Discussion

Localized amyloidosis of the penis has been reported previously[1], but we are aware of only four cases involving the glans[2,3] and report what is believed to be the fifth Amyloidosis is worth considering in the differential diagnosis of an apparent carcinoma of the glans, particularly in a young man Local excision has been adequate, in most cases, although the patient described by Bodner *et al*[2] showed locally extensive disease that required wider excision

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Surgical workshop

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End-to-end anastomosis involving vessels of different diameters

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An end-to-end anastomosis between two vessels of different diameters often creates anastomotic kinking, especially if one of the vessels is a prosthesis. Because of lack of prosthesis elasticity, the anastomosis may be carried out by spatulating the venous tissue only. This situation may happen in the intermediate anastomosis of a composite femoropopliteal bypass. A technique of end-to-end anastomosis that is more favourable haemodynamically has recently been described[1]. It allows the vascular axis to remain straight in spite of differences in diameter between prosthesis (large vessel) and vein (small vessel). The technical steps in the construction of this anastomosis have not been described previously and are detailed here.

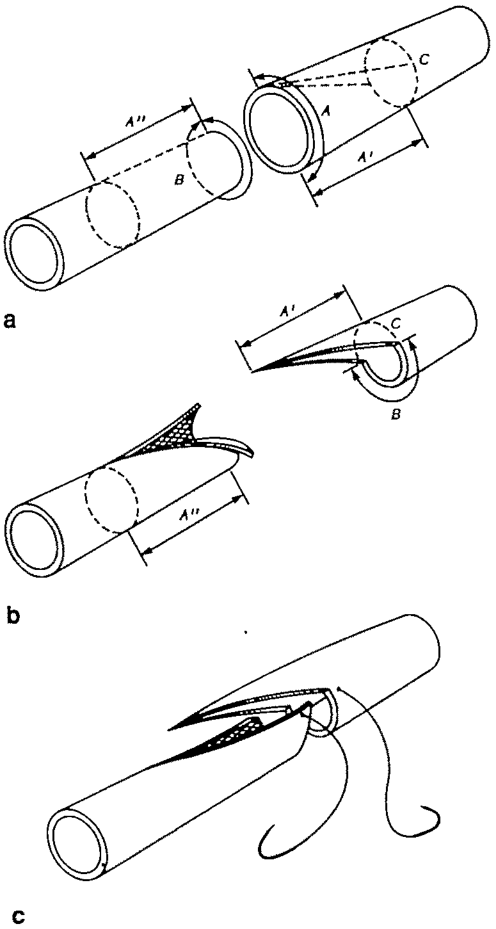

Figure 1 *Theoretical steps of the anastomosis*

Technique

The technique converts the anastomotic zone into a truncated cone, the small diameter of which equals that of the vein and the large one that of the prosthesis. The vein is opened longitudinally and part of the prosthesis circumference is bevelled. The incisions on the vein and on the bevel are of the same length.

In theory, the distances involved in performing the end-to-end anastomosis are, respectively, half the prosthesis circumference (*A*) and the circumference of the vein (*B*) (*Figure 1a*). Distance *A* is measured along the prosthesis (*A′*), determining a theoretical circumference *C* that represents the base of the bevel (dotted lines) joining the end of the prosthesis. Distance *A* is also measured along the vein (*A″*). The vein is then opened along this distance. On the prosthesis, the bevel is prepared (*Figure 1b*); its base corresponds to part of the circumference *C*. The remaining part of the circumference *C* is equal to *B*, in other words, the circumference of the vein. The bevel is adapted to the longitudinal incision on the vein and the extremity of the latter to the corresponding segment of the prosthesis (*Figure 1c*).

The operative technique is simple. The end of the prosthesis is flattened and folded over so that it coincides with one of the sides (*Figure 2a*). In this position, the free edge is cut, providing an opening equal in length to half the prosthesis circumference (*Figure 2b*). Next,

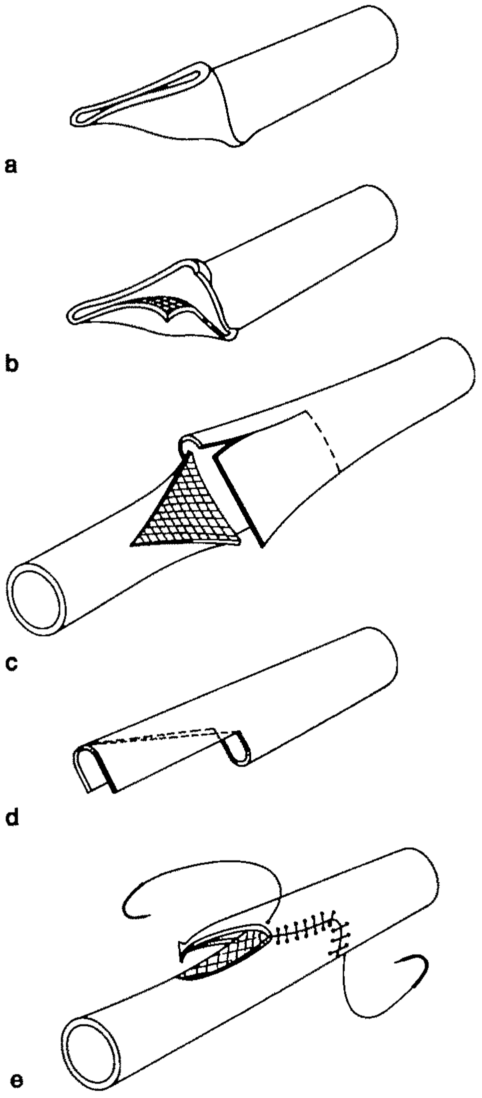

Figure 2 *Technical steps of the anastomosis*

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the vein is opened longitudinally for the same length, and spread along the prolongation of the flattened prosthesis (*Figure 2c*). The prosthesis is cut along the prolongation of an edge of the cut vein, so that a flap may be lifted up. One edge of the flap is equal therefore to half the circumference of the prosthesis, while the other is equal to the circumference of the vein. The flap is excised. The prosthesis in the flattened position is then rolled up (*Figure 2d*) and bevelled (along the dotted lines). The extremity of the bevel is excised to round it off, making suturing around the corner easier (*Figure 2e*). The anastomosis is carried out with a running vascular suture.

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Case report

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Unprecipitated rupture of the brachiocephalic artery during repeated surgery for parathyroid carcinoma

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Parathyroid carcinoma is a rare cause of primary hyperparathyroidism. Despite increasing reporting of cases[1] over the past 20 years, an individual surgeon's experience of this disease is limited, particularly in relation to complications of repeated surgery in such patients.

The best results are achieved by adequate excision at the first operation, but occasionally the malignant component is not recognized at this stage and the patient returns over a period of years for further excision of neoplastic tissue from the neck and mediastinum.

Two such patients are presented who developed an identical previously unreported complication of repeated parathyroid cancer excision.

Case reports

Patient 1

In 1987 a 58-year-old man presented with renal calculous disease, was found to be hypercalcaemic (calcium level 3.0 mmol/l) and was diagnosed as having primary hyperparathyroidism (parathyroid hormone concentration 0.76 ng/ml). Neck exploration was undertaken and one enlarged parathyroid gland excised from the right inferior position; the remaining glands appeared normal. The enlarged gland was reported histologically as an adenoma.

The patient presented again 20 months later with a lump in the scar that, when excised, proved to be parathyroid carcinoma. The serum calcium level was 3.4 mmol/l and further neck exploration was undertaken. Locally infiltrating carcinoma was encountered, which was excised radically by total thyroidectomy, thymectomy, excision of the right internal jugular nodes, and sacrifice of the right recurrent laryngeal nerve.

After a further 14 months the serum calcium concentration had risen to 3.7 mmol/l. At further operation there was no evidence of neoplasm in the neck but recurrent tumour was present adjacent to the brachiocephalic artery in the superior mediastinum. As this tissue was being dissected with no direct manipulation of the arterial trunk, the artery spontaneously ruptured. The brachiocephalic artery was therefore transected proximal to the defect and the carotid and subclavian arteries divided after vascular control had been achieved. A Y shaped polytetrafluoroethylene (PTFE) graft was used to repair the defect.

The patient developed left hemiplegia 2 days later and died 1 week later from bronchopneumonia. Post-mortem examination confirmed thrombotic occlusion of the carotid limb of the graft.

Patient 2

A 60-year-old man presented in 1979 with constipation and polydipsia. The serum calcium level was 3.1 mmol/l and the parathyroid hormone concentration was raised. At parathyroidectomy an enlarged right inferior gland was removed; histological examination confirmed a parathyroid adenoma.

The patient presented again 8 years later with similar symptoms and a serum calcium level of 3.7 mmol/l. At repeat operation, locally invasive carcinoma was found in the neck; this was excised and normocalcaemia achieved.

The patient's serum calcium level was again grossly raised after a further year, necessitating further exploration of the neck and mediastinum. Total thyroidectomy, thymectomy, node clearance and excision of the right recurrent laryngeal nerve achieved normocalcaemia. Despite medical treatment designed to reduce recurrent hypercalcaemia, further exploration was undertaken 1 year later. Again, extensive tumour in the superior mediastinum was found, which was dissected from around and behind the great vessels. During gentle traction the brachiocephalic artery ruptured. After resection of the ruptured arterial ends an interpositional PTFE graft was used to repair the defect. Histological examination showed no direct invasion of the artery with tumour. The patient died 4 months later from hypercalcaemia but with no arterial complication.

Discussion

Ideally, parathyroid carcinoma should be completely excised at initial operation but it often goes unrecognized at this time or is partially irresectable, creating the need for repeated neck and mediastinal surgery to remove recurrent disease. As demonstrated by the patients reported, the cancer tends to progress into the superior mediastinum and can be found adjacent to or surrounding the great vessels. Qvist *et al*.[2] have reported one case in which the brachiocephalic artery was resected at initial mediastinal exploration to facilitate tumour clearance, with vascular reconstruction. There appear to be no reports of rupture of the vessels at mediastinal dissection when not subjected to direct trauma.

The brachiocephalic artery is relatively unsupported if the surrounding tissue is excised and, if already weakened by having been encased in neoplastic or inflammatory tissue, may rupture on the slightest provocation, even in the absence of direct invasion into the arterial wall.

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Parotidectomy for parotid tumours: 19-year experience from the Netherlands

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A total of 150 patients were treated for parotid tumours over a period of 19 years. In 94 per cent superficial or total parotidectomy was performed. Histological diagnosis of the resected specimen revealed pleomorphic adenoma in 92 patients (61 per cent), Whartin's tumour in 30 (20 per cent), various benign neoplasms in 11 (7 per cent) and malignant tumour in 17 (11 per cent). After a mean follow-up of 7·7 years, no recurrence of a benign tumour was seen. Malignant tumours recurred in five patients. Permanent partial facial paralysis was seen in 4 per cent of patients after surgery for benign lesions. Frey's syndrome was observed in 43 per cent of patients, and was not prevented by resection of the auriculotemporal nerve.

Tumours of the parotid gland are uncommon, the estimated incidence[1,2] ranging between 1 and 3 per 100000 per year. Uncertainty exists over the optimal treatment of such tumours, some favouring conservative surgery followed by radiotherapy, others preferring parotidectomy as the treatment of choice[3,4] Although parotidectomy is currently the generally recommended therapeutic option for all parotid tumours, a recent review of clinical practice in the UK revealed that local excision of such tumours is still commonly performed[2].

Parotidectomy has been the treatment of choice for parotid tumours in this institution, and this report gives details of this experience over the past 19 years.

Patients and methods

Records of all those undergoing surgery for a parotid mass at this hospital during the period 1972–1990 were reviewed. Missing and follow-up data were obtained by questioning the patients by telephone or questionnaire.

In 150 patients undergoing operation for a parotid mass, 142 procedures were performed by one surgeon (J D.K.M.).

Follow-up data were obtained from 116 patients with a mean follow-up of 7·7 (range 1·0–18·6) years Recent data were not obtained from 34 patients: 15 had died and 19 could not be contacted.

Results

Figure 1 shows the final diagnosis after histological examination of the resected parotid mass for all 150 patients. The histological diagnosis of malignant tumours according to the World Health Organization International Classification[5] is shown in *Table 1*. The median age of patients with a pleomorphic adenoma was 43 (range 14–77) years; the median age of those with Whartin's tumour was 61 (range 39–76) years. This tumour occurred predominantly in men, the male:female ratio being 6·5:1.

Symptoms

Preoperative symptoms leading to parotid surgery were a growing mass and pain. Growth of the mass was found equally in patients with a pleomorphic adenoma (57 per cent), Whartin's tumour (52 per cent) or a malignant tumour (53 per cent). Pain was a major symptom in patients with a malignancy (35 per cent), but occurred less frequently in those with a pleomorphic adenoma (8 per cent) or Whartin's tumour (17 per cent). Paralysis of the facial nerve before surgery occurred in one patient with an undifferentiated carcinoma. The median duration of swelling before surgery was 24 months for pleomorphic adenoma, 12 months for Whartin's tumour and 5 months for malignant tumour.

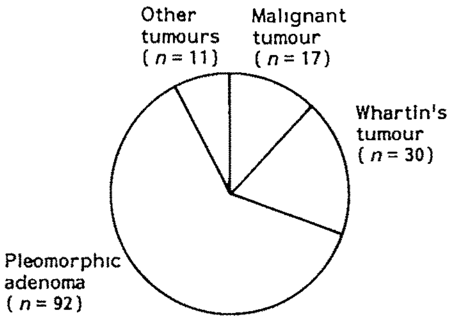

Figure 1 *Histological diagnosis of parotid tumours. Values are numbers of patients*

Table 1 *Histological diagnosis of malignant tumours in 17 patients*

Diagnosis	No. of patients
Adenocarcinoma	2
Adenoid cystic carcinoma	2
Undifferentiated carcinoma	3
Squamous cell carcinoma	2
Carcinoma in pleomorphic adenoma	1
Acinic cell carcinoma	2
Mucoepidermoid carcinoma	1
Malignant lymphoma	4

Table 2 *Results of preoperative examination*

Examination	No of patients*	Result	
		Positive	Negative
Sialography	89	59 (66)	30 (34)
Scintigraphy	32	28 (88)	4 (12)
Computed tomography	48	44 (92)	4 (8)
Aspiration cytology	35	26 (74)	9 (26)

Values in parentheses are percentages *Number in whom the results of examination could be traced

Diagnosis

Table 2 shows the results of preoperative examination. Aspiration cytology correctly predicted the diagnosis in 17 of 21 patients (81 per cent) with a pleomorphic adenoma.

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Table 3 *Operations performed*

	Type of parotidectomy			
Diagnosis	Superficial	Total	Partial	Total
Pleomorphic adenoma	71	16	5	92
Warthin's tumour	29	0	1	30
Malignant tumour	10	5	2	17
Other tumours	9	1	1	11

Table 4 *Frey's syndrome*

	Auriculotemporal nerve resection	
Frey's syndrome	Performed	Not performed
Present	38	26
Absent	48	25

The presence or absence of Frey's syndrome was unknown in four patients undergoing resection of the auriculotemporal nerve and in nine in whom this was not performed $\chi^2 = 0{\cdot}59$, 1 d.f., $P > 0{\cdot}5$

Operation

The type of operation performed in relation to the final pathological diagnosis is shown in *Table 3* Thirteen patients with a malignant tumour received radiotherapy and one with an adenocarcinoma underwent radical neck dissection In nine patients a peroperative frozen section examination of the tumour was performed, and in seven the diagnosis from this was correct

Complications

Complications in the immediate postoperative period were a haematoma or seroma in seven patients (5 per cent), wound infection in three (2 per cent) and a temporary salivary fistula in four (3 per cent).

After operation, 106 patients (71 per cent) had partial or total paralysis of the facial nerve This was temporary in 76 patients (72 per cent), permanent in 11 (10 per cent) and in 19 (18 per cent) of unknown duration. The median duration of temporary paralysis was 3 months. Permanent paralysis occurred most frequently after surgery for malignant tumours (six of 17 *versus* five of 133), and in four patients the facial nerve was resected and replaced by a sural nerve transplant. The global palsy partially recovered in all patients. Permanent partial facial paralysis after resection of benign lesions was attributed to intraoperative damage of one or more fascicles in four of five patients. In these patients the palsy was partial, affecting primarily the mouth area

Frey's syndrome was seen in 64 patients (43 per cent). To prevent the development of this syndrome the auriculotemporal nerve was resected in 90 patients. *Table 4* shows the incidence of Frey's syndrome related to resection of the auriculotemporal nerve

Nineteen patients (13 per cent) had a painful scar, sometimes accompanied by a neuroma of the greater auricular nerve This nerve was saved in 65 per cent of patients, thereby avoiding loss of sensation in the ear lobe.

Recurrence

In five patients the original malignant tumour recurred, no recurrence of a benign neoplasm was reported.

Discussion

The de Wever Hospital is a large regional centre serving a population of approximately 200 000–250 000, no patient came from outside the region The estimated incidence of parotid tumours was 3·2–3·9 per 100 000 per year, which is higher than that reported by others[2,6], but in agreement with the incidence of 4 per 100 000 per year reported by Lennox *et al* for eastern Scotland[7].

The proportion of malignant tumours (11 per cent) was lower than that reported by others[8,10] Over-representation of malignant tumours in other series may derive from specialist referral.

Computed tomography (CT) proved to be the most accurate preoperative method of examination. Magnetic resonance imaging, which is reported to give more detailed anatomical information and to define the position of a parotid mass relative to the facial nerve better[11–13], may surpass CT Sialography has been replaced by CT, scintigraphy may be useful in that Warthin's tumours take up technetium-99m pertechnetate.

The sensitivity of fine-needle aspiration cytology was 74 per cent for all tumours in which it was performed and 81 per cent for pleomorphic adenoma, these results are comparable to those obtained by others[10] Failure of aspiration cytology to give an accurate diagnosis was attributed to insufficient material in the biopsy specimen in six of nine patients

The sensitivity of peroperative frozen section examination was only 78 per cent, but this method is known to be associated with false-negative results in 5–25 per cent of cases[14,15].

Superficial or total parotidectomy was performed in 94 per cent of patients. All benign tumours were completely excised and, after a mean follow-up of 7·7 years, no recurrence has occurred. Excision of the lesion with sufficiently wide tumour-free margins precludes recurrence. Rates for recurrence of pleomorphic adenoma range between 3 and 8 per cent for enucleation with radiotherapy[3,16], and zero and 2 per cent for parotidectomy[4,17,18] Five malignant tumours recurred despite postoperative radiotherapy, two tumours were incompletely excised and in two tumour spilling occurred

Those who advocate enucleation or limited resection of benign parotid tumours in combination with radiotherapy argue that this reduces the incidence of complications, especially facial nerve injury. Eleven patients (7 per cent) had an established permanent facial paralysis, six having a malignant and five a benign lesion. Permanent facial paralysis occurred in 4 per cent of patients with benign tumours, comparable to other results[8,9,17–19] Permanent facial paralysis in four of five patients was attributed to deliberate sacrifice of one or more fascicles to permit radical tumour excision. In all these patients facial paralysis was partial, resulting in only minor disability.

Peroperative resection of the auriculotemporal nerve did not lower the incidence of gustatory sweating resection of the auriculotemporal nerve to prevent Frey's syndrome is not justified Symptoms were mild in almost all patients and could be alleviated by topical application of an anticholinergic agent[20].

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Case report

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Muir–Torre syndrome with multiple neoplasia

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The association of sebaceous gland tumours with internal malignancies was first described by Muir *et al.*[1] in 1967 and Torre[2] in 1968. A recent review[3] revealed that 120 cases have been reported fulfilling the diagnostic criteria for Muir–Torre syndrome. A case remarkable for presenting the highest number of malignancies described in this syndrome (ten) and a prolonged survival of 19 years is reported.

Case report

In 1989 a 53-year-old man came to this department with a diagnosis of rectal carcinoma. A mass was palpable 6 cm from the anal margin and colonoscopy showed a sigmoid polyp at 15 cm. The patient also had psoriasis and hidradenitis. Abdominoperineal resection was performed, and pathological examination showed a Dukes' B adenocarcinoma plus an adenomatous polyp.

On review of the history, this patient had undergone right hemicolectomy at another hospital in 1972 for undifferentiated Dukes' B adenocarcinoma. In 1978 segmental right ureterectomy was performed for transitional cell carcinoma ($T_1 N_0 M_0$) In 1983 a sebaceous epithelioma had been resected from the left thigh Between 1986 and 1987 four urological operations were performed at this hospital for low-grade tumours· partial excision of the right renal pelvis, segmental left ureterectomy and two transurethral resections at the right ureteric meatus. A fifth operation in 1987 for invasive carcinoma ($T_{3a} N_0 M_0$) entailed radical right nephroureterectomy.

Several family members had a history of malignancy. The patient's mother and one brother had died at the age of 75 and 60 years respectively from gastrointestinal carcinoma. Another brother has been operated on for colorectal cancer

Repeat colonoscopy 16 months after abdominoperineal resection showed metachronous carcinoma 20 cm from the stoma. Total colectomy was performed with end ileostomy for adenocarcinoma in a tubulovillous adenoma. At follow-up 12 months after the last operation, ileal endoscopy and abdominal ultrasonography results were normal. The carcinoembryonic antigen level has not increased, there has been no recurrence of urinary tract neoplasia and no new skin lesions Despite the autosomal dominant inheritance of the syndrome[4], none of the patient's children has developed tumours

Discussion

The Muir–Torre syndrome is the association of sebaceous gland tumours with internal malignancies, such as of the colorectum (47 per cent), genitourinary tract (21 per cent), breast (12 per cent) and blood (9 per cent). A report has been presented of a patient with three colorectal adenocarcinomas, one sebaceous epithelioma and six urinary tract carcinomas at different sites and of varying malignancy. This case reveals the indolent course of multiple neoplasia in patients with Muir–Torre syndrome and the prolonged survival that is possible after surgical treatment. It also shows the importance of screening for cancer in all patients and relatives with these uncommon sebaceous gland tumours[5].

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Meal area index: a new technique for quantitative assessment in achalasia by ambulatory manometry during eating

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Ambulatory non-perfused oesophageal manometry was used to study oesophageal body function during consumption of a full meal in patients with achalasia. A measure of oesophageal body activity (the meal area index) was developed by calculating the total area under the pressure curve during eating, above the preprandial baseline oesophageal pressure, per meal minute. Untreated patients with achalasia ($n = 13$) *were compared with normal subjects* ($n = 42$), *patients with benign stricture* ($n = 9$) *and patients with achalasia who had undergone Heller's myotomy* ($n = 17$). *The results showed a high meal area index in achalasia, due to a rise in baseline oesophageal pressure and frequent high-amplitude contractions during eating. This was not seen in normal subjects or patients with stricture. The high meal area index was abolished by successful Heller's myotomy but remained in two patients with persisting dysphagia. Sustained high intraoesophageal pressure is generated during consumption of a solid meal in untreated achalasia, resulting in a unique manometric profile. Manometry during eating using the meal area index permits quantitative assessment of oesophageal body function in achalasia and may aid in the assessment of response to treatment.*

Traditional manometric evaluation of the oesophagus in achalasia demonstrates raised resting oesophageal pressure, absence of peristaltic contractions in the body of the oesophagus, and failure of the lower oesophageal sphincter (LOS) to relax on deglutition[1]. Following successful treatment, the LOS and resting oesophageal body pressures are reduced[2]. There is usually no difference in the response of the oesophageal body to deglutition, although there are reported cases of return of normal peristalsis. There is, however, poor correlation between either the LOS or the resting oesophageal pressure and clinical symptoms[3]. Traditional manometry is of little or no value in the assessment of the patient with persisting or recurrent symptoms after treatment.

Patients with achalasia experience symptoms while eating solid meals, but traditional manometry investigates oesophageal function in a fasted supine patient who swallows water boluses on command. Reliable non-perfused ambulatory manometry systems have recently been developed. Using ambulatory oesophageal manometry during the consumption of a solid meal, the response of the oesophageal body to eating has been investigated in patients with achalasia. Based on these manometric findings, a new objective measure of oesophageal body activity, the meal area index, has been developed. This measure allows quantification of the influence of Heller's myotomy on oesophageal body function in achalasia. The meal area index can also be correlated with clinical status. For comparative purposes, measurements were made in normal subjects and in patients with dysphagia due to benign oesophageal stricture.

Patients and methods

Eighty-one subjects were studied. Thirteen patients had untreated achalasia and 17 were studied after undergoing Heller's myotomy. All patients with achalasia had previously undergone 24-h ambulatory pH studies, endoscopy, barium swallow and stationary perfused oesophageal manometry Achalasia was diagnosed using the manometric criteria of the absence of peristalsis within the oesophageal body and failure of the LOS to relax in response to swallows, and exclusion of other gastro-oesophageal disease There was no patient with vigorous achalasia.

Nine patients with benign oesophageal stricture secondary to chronic gastro-oesophageal reflux disease were studied before stricture dilatation; one had a markedly dilated oesophagus above the stricture. Forty-two normal subjects were also studied. 12 were volunteers and the remaining 30 were patients with chest pain of non-cardiac origin in whom all oesophageal investigation results were normal. None complained of dysphagia. Each of these 30 patients had normal results from upper gastrointestinal endoscopy, 24-h ambulatory oesophageal pH monitoring, edrophonium provocation testing and stationary perfused manometry None of the normal subjects had diabetes mellitus, alcoholism, collagen vascular disorders or neurological disease.

Ambulatory oesophageal manometry

Oesophageal manometry was performed with the subject fully ambulant. A non-perfused system was used. A two-channel solid-state recorder (Synectics, Stockholm, Sweden) was used, this was capable of continuous measurement for 4 h at a sampling frequency of 8 Hz. A silicone-sheathed catheter with two microtransducers mounted 5 cm apart (Gaeltec Research, Isle of Skye, UK) was connected to this recorder, inserted through the nose and positioned with the transducers 5 and 10 cm above the upper limit of the LOS. All studies were performed after an overnight fast. After an acclimatization period of 30 min, the patient ate a standardized test meal, removed from the stress of the laboratory environment The test meal constituents are shown in *Table 1*; 250 ml water was allowed with it, the patient depressing an event marker to signal the start and end of the meal. No alteration was made to the patients' normal patterns of eating, but they were asked to eat all of the meal. The recording was continued for 1 h into the postprandial period and the data then loaded on to a personal computer. Analysis was performed using Gastrosoft software, Motilitygram version 1 98 (Synectics).

In the analysis, three features of the manometric profile during eating were documented: the pattern of motility (i e. the presence or absence of propagated peristaltic waves); any alteration of the baseline intraoesophageal pressure, and the total area under the pressure curve

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Table 1 *Test meal constituents*

Food	Portion	kCal (kJ)	Protein (g)	Fat (g)	Carbohydrate (g)	Fibre (g)
Roast chicken	90 g	135 (564)	22·3	4·9	—	—
Mashed potatoes	150 g	180 (752)	2·2	7·5	27·0	1·4
Mashed carrots	90 g	20 (84)	0·5	—	3·9	2·8
Tinned pears	100 g	46 (192)	0·5	—	20·0	2·3
Custard	150 ml	177 (740)	5·7	6·6	25·2	—
Total		558 (2332)	31·2	19·0	76·1	6·5

above the immediate preprandial intraoesophageal baseline pressure. The area under the pressure curve was determined by the computer software using Simpson's integration formula. In addition, the time in minutes taken to eat the meal was measured. A mean total area under the pressure curve was calculated from the readings 5 and 10 cm above the LOS. To allow interpatient comparison, this mean was divided by the meal duration (*Figure 1*). A single measurement for each patient was therefore derived; this is referred to as the meal area index.

Statistical analysis

Results are presented as median (range). The significance of differences in median values was determined by the Mann–Whitney rank sum test for unpaired non-parametric data.

Results

Normal subjects

Propagated peristalsis was present during eating in both asymptomatic volunteers and normal patients (*Figure 2*). There was no significant difference between the two groups. The peristaltic waves were single or double peaked, with a median amplitude of 52 (range 24–100) mmHg. Throughout the meal period, there was no sustained change in the baseline intraoesophageal pressure in any of the normal subjects. The median meal area index in normal subjects was 232 (range 30–575) (*Figure 3*).

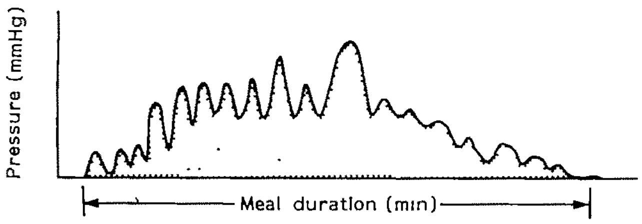

Figure 1 *Calculation of the meal area index,* A/T. A, *area under the curve;* T, *test meal duration*

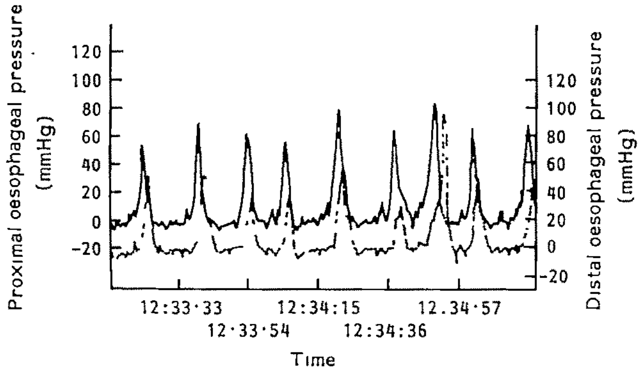

Figure 2 *Ambulatory oesophageal body manometry during eating in a normal subject.* ——, *Proximal oesophageal pressure,* ··, *distal oesophageal pressure*

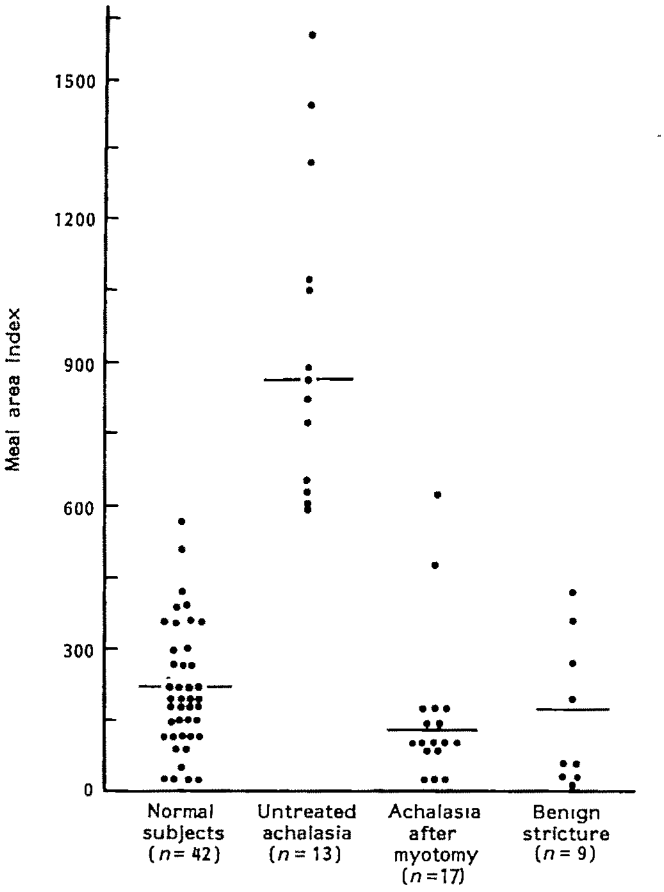

Figure 3 *Meal area index in the patient groups. Bars are median values. The difference between the untreated achalasia group and each of the other groups was significant* (P < 0·001, *Mann–Whitney rank sum test for unpaired data*)

Untreated patients with achalasia

Patients with achalasia demonstrated a unique pattern on manometry during the meal period (*Figure 4*). Shortly after the start of the meal, there was a gradual increase in the baseline intraoesophageal pressure. Usually, this raised pressure was sustained throughout the meal and into the early postprandial period. Occasionally during the meal, however, the intraoesophageal pressure fell towards the preprandial level, only to rise again later. The median rise in the intraoesophageal pressure above the preprandial level was 40 (range 30–75) mmHg. This sustained rise in baseline intraoesophageal pressure was not observed in the other patient groups. Superimposed on the high baseline pressure, there were frequent prolonged multipeaked non-peristaltic contractions. None of these patients was considered on stationary manometry to have vigorous achalasia, yet the median peak pressure during eating was 90 (range 65–120) mmHg. Two patients had evidence of propagated peristaltic waves during eating. This is in contrast

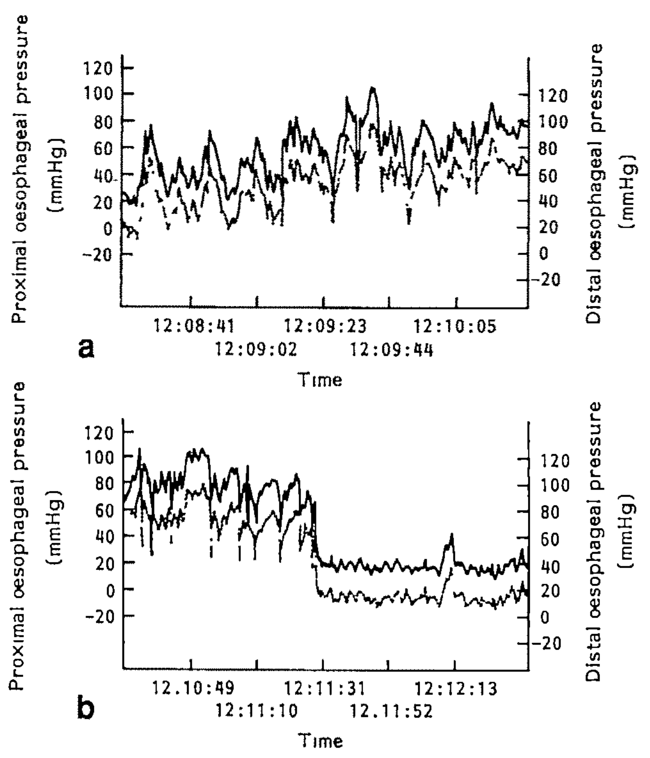

Figure 4 *Ambulatory oesophageal body manometry during eating in an untreated patient with achalasia. ——, Proximal oesophageal pressure, ····, distal oesophageal pressure* **a** *Typical pattern,* **b** *postprandial period*

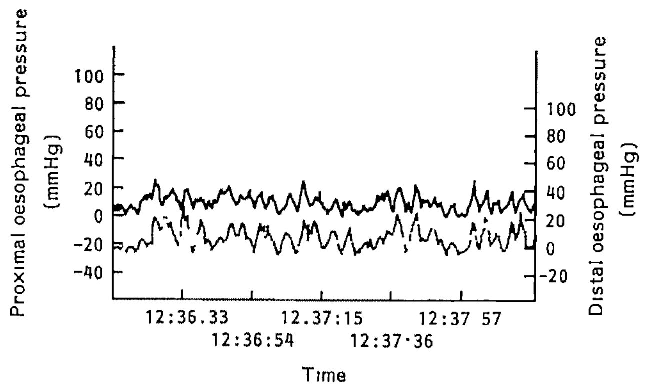

Figure 5 *Ambulatory oesophageal body manometry during eating in achalasia after successful Heller's myotomy. ——, Proximal oesophageal pressure; ···, distal oesophageal pressure*

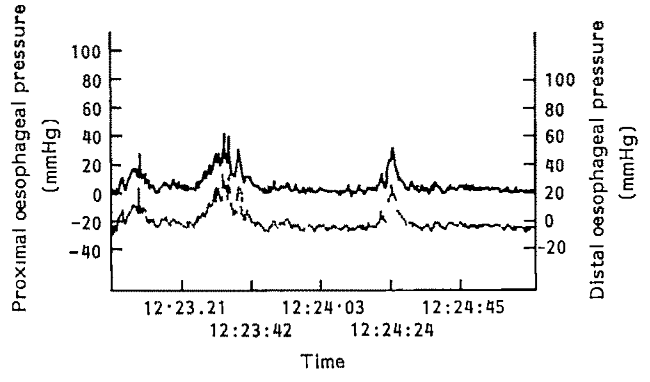

Figure 6 *Ambulatory oesophageal body manometry during eating in a patient with a benign oesophageal stricture. ——, Proximal oesophageal pressure, · ··, distal oesophageal pressure*

to the findings at stationary perfused manometry in both of these patients, where all contractions recorded were simultaneous.

The combination of the sustained rise in the baseline intraoesophageal pressure and the oesophageal contractions resulted in the intraoesophageal pressure being maintained between 40 and 90 mmHg for almost the entire meal and in some cases well into the postprandial period. As a result, the total area under the pressure curve above the preprandial baseline pressure was greatly raised in the untreated patients with achalasia. The median meal area index was 895 (range 588–1681) (*Figure 3*). There was no overlap between indices of patients with achalasia and normal subjects ($P < 0.001$).

Patients with achalasia after Heller's myotomy

Successful Heller's myotomy abolished both the rise in intraoesophageal pressure during the meal and the frequent high-amplitude aperistaltic contractions (*Figure 5*). As a result, there was no difference between the ambulatory manometry during the meal and the standard stationary perfused manometry. The baseline intraoesophageal pressure remained constant throughout the meal and the contractions observed were all of low amplitude, and so the total area under the pressure curve above the preprandial baseline intraoesophageal pressure was low The median meal area index was 139 (range 12–614) (*Figure 3*). This was significantly lower than the index in the untreated achalasia group ($P < 0.001$). There was no evidence of a return of peristalsis within the oesophageal body during eating following Heller's myotomy.

There were two patients with persistent dysphagia after Heller's myotomy; both demonstrated a rise in baseline intraoesophageal pressure during eating and had evidence of high-amplitude contractions. The result was a meal area index of 475 in one and 614 in the other, values approaching those seen in the untreated achalasia group. The remaining 15 patients studied after Heller's myotomy were asymptomatic and the highest meal area index observed in these was 190. Following a second myotomy, which was successful, the meal area index fell from 475 to 150 in the one patient studied a second time. A 24-h pH record was taken in 15 of 17 patients after Heller's myotomy. All 15 were normal, i.e. the proportion of the total time at pH < 4·0 was under 6 per cent.

Patients with benign stricture

None of the patients with benign stricture demonstrated a rise in intraoesophageal baseline pressure during the meal. Even the patient with a grossly dilated oesophagus above a long-standing stricture did not show any change in the baseline pressure during eating (*Figure 6*). In this respect, these patients differed from those with untreated achalasia. Most often there were simultaneous low-amplitude contractions present, although three patients demonstrated propagated peristalsis during eating. As a result of the low-amplitude pressure waves and the absence of any rise in the baseline intraoesophageal pressure, the total area under the pressure curve tended to be low. The median meal area index was 180 (range 30–440) (*Figure 3*). One patient with decompensated megaoesophagus had an index of 66.

Discussion

Achalasia is characterized by a failure of the LOS to relax in response to swallowing. In addition, there is absence of propagated peristalsis within the oesophageal body. It is likely that a selective degeneration of the non-cholinergic non-adrenergic inhibitory neurones is responsible. Stationary perfused oesophageal manometry is used to establish the diagnosis. The manometric findings within the oesophageal body seem to imply that the latter is flaccid and dilates passively as a result of stasis. However, it is difficult to reconcile the oesophageal body findings in classical achalasia with those of vigorous achalasia, in which high-amplitude contractions are recorded. Furthermore, oesophageal scintigraphy in achalasia demonstrates active shuttling of radiolabelled isotope within the oesophagus. The oesophageal body in achalasia demonstrates an exaggerated response to catecholamines. These observations raise the possibility that the manometric findings within the oesophageal body in achalasia represent an artefact of the manometry technique employed. The use of a fine-bore manometry catheter within a dilated oesophagus is likely to result in any pressure phenomenon being damped, thereby explaining the low-amplitude contractions observed.

The manometric profile obtained in achalasia during consumption of a full solid meal results in a very different impression of intraoesophageal events compared with traditional oesophageal manometry. Typically, the response of the oesophageal body in achalasia to controlled wet and dry swallows is simultaneous low-amplitude contractions. In contrast, during eating the oesophageal body in achalasia generates high pressures, which are sustained and persist into the postprandial period. This phenomenon has not been previously reported and is unique to achalasia in our experience. It is interesting that two of the patients with achalasia studied showed evidence of propagated waves during the meal. It would appear that the presence of the meal within the oesophagus is required before these pressure patterns can be detected. The pressures cannot be explained as merely reflecting the accumulation of food, as none of the patients with benign stricture demonstrated this sustained rise in pressure during the meal. Long-standing organic obstruction of the lower oesophagus appears to be associated with an oesophageal body unable to generate high pressures and that subsequently dilates passively. Furthermore, the pressure profile observed in achalasia during eating consisted of two components: high-amplitude contractions superimposed on a raised baseline pressure. These contractions cannot be explained by the passive accumulation of food within the oesophageal body. It appears that during the prandial and early postprandial periods there is sustained activity within the oesophageal body, possibly in an attempt to overcome the failure of the LOS to relax. This activity, however, is not well coordinated and the contractions are simultaneous. This finding helps to explain the poorly understood shuttling of retained isotope within the oesophageal body during scintigraphy in patients with achalasia[4]. The oesophageal body in achalasia displays features more in keeping with denervation hypersensitivity than with the old concept of hypomotility, when studied during eating.

Patients with achalasia usually experience symptoms in relation to eating. The limitations imposed by perfused manometry explain why the oesophagus has rarely been studied during eating. The development of ambulatory non-perfused oesophageal manometry in recent years has made it feasible to investigate oesophageal motility in a wide variety of settings, outside the potentially stressful laboratory, during the consumption of a solid meal. Ambulatory oesophageal manometry has been widely studied in patients with non-cardiac chest pain, with varying success[5–7]. Most workers have concentrated on the association between manometric abnormalities and episodes of chest pain; very few studies have looked specifically at oesophageal manometry during eating[8–10]. Howard *et al.*[9] and Mellow[8] found a poor relationship between results of conventional manometry and fed patterns of oesophageal motility. They found a high incidence of non-conducted swallows and synchronous contractions during eating in both normal volunteers and patients. Oesophageal dysmotility was accentuated during eating; neither study investigated patients with achalasia. Little *et al.*[10] have provided the only previous description of the response of the oesophageal body during eating in patients with achalasia. In the eight patients with untreated achalasia studied there was a rise in the baseline oesophageal pressure and an increased number of simultaneous oesophageal contractions. The rise in the baseline pressure (5–10 mmHg) and the amplitude of the simultaneous contractions were considerably less than those observed in the present series. No difference was reported in the amplitude of the contractions during eating compared with those observed during standard manometry, the differences observed relating only to frequency[10]. This probably represents differences in the manometric technique and in the constituents of the test meal. Little *et al.* did not state whether the test meal was standardized and did not present the constituents of the meal.

Assessment of treatment in achalasia is difficult and commonly based on the patient's symptoms. More objective criteria, including LOS pressure[2,11], oesophageal diameter[12], height of a barium column above the LOS on barium swallow[13,14] and endoscopic appearance of the gastro-oesophageal junction[15], have all been suggested. Reduction in LOS pressure has been found to correlate poorly with symptoms and with results of other tests of oesophageal function such as radionuclide imaging[3,16]. Agha and Lee[14] reported good correlation between radiological features and dysphagia; Ott *et al.*, however, concluded that radiological appearance is a poor predictor of patient response[17]. Measuring oesophageal emptying with radionuclide imaging overcomes some of these problems. Although it has been shown that there is a correlation between percentage change in oesophageal emptying and improvement in symptoms after treatment in achalasia, there is such a scatter that it is not possible to select a level of improvement in emptying that accurately predicts success in an individual patient[3,18]. It appears that symptoms are not related to the absolute degree of oesophageal obstruction, but probably reflect other factors such as the patient's tolerance and dietary adaptations.

The present study has developed a new objective assessment of oesophageal body function, the meal area index. In patients with achalasia, this measurement combines the observed effect of the rise in the baseline oesophageal pressure during eating with the frequent high-amplitude oesophageal body contractions. The meal area index was of use in assessing the response to myotomy. It correlated excellently with symptoms. The two patients with recurrent dysphagia both had a high meal area index. None of the patients studied, however, represented a difficult clinical problem in terms of assessment. In particular, none had evidence of abnormal gastro-oesophageal reflux on 24-h oesophageal pH monitoring. The value of the meal area index remains to be determined in the assessment of patients after pneumatic dilatation or with evidence of gastro-oesophageal reflux as a result of treatment.

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Laparoscopic orchidectomy in cryptorchidism

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In patients with an undescended testis, it has been found that the testis is intra-abdominal in 2 per cent and absent in a further 0·6 per cent[1]. At present these patients are treated by orchidectomy at open operation after localization by laparoscopy. Two cases of laparoscopic orchidectomy are described.

Surgical technique

Two patients (aged 25 and 33 years) were found, while being investigated for unrelated conditions, to have an impalpable testis The opposite testis was normal in size and consistency. Abdominal and inguinal ultrasonography did not demonstrate the site of the missing testis.

Under general anaesthesia, pneumoperitoneum was established and a 10-mm cannula and telescope were inserted immediately below the umbilicus In both patients an atrophic testis was found in the abdomen at the lateral pelvic wall Two 5-mm ports were established, one in the ipsilateral iliac fossa and a second suprapubically The testis was mobilized and the testicular vessels were clipped. The testis was then removed through the 10-mm cannula, and the incisions were closed with single sutures. Both patients returned home the following morning

Histological examination of the testes revealed testicular atrophy with no spermatogenesis

Discussion

Few intra-abdominal testes are suitable for revascularization followed by orchidopexy to place the testis in the scrotum[2]. Most are atrophic with little spermatogenic potential and carry a 20–100-fold increase in the risk of developing testicular cancer[3], making excision essential.

Laparoscopy has a clear role in the location of an impalpable testis[4]. The laparoscopic approach to excision in patients after puberty offers the advantage of combining the localization and therapeutic procedures without the need for a separate incision. Only one other case of laparoscopic orchidectomy has been described[5], but it is likely that the technique could be performed as a daycase and may reduce both inpatient stay and time off work.

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Laser recanalization *versus* endoscopic intubation in the palliation of malignant dysphagia: a randomized prospective study

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Forty patients with histologically confirmed malignant dysphagia were randomized to either endoscopic intubation or laser recanalization. Age, sex, tumour histology and site were evenly distributed between the groups. Results were analysed on an 'intention to treat' basis. All patients treated by laser achieved patency; there was one failed intubation. The best swallowing grade achieved was significantly better with laser recanalization (median 4 (range 3–4)) than with intubation (median 3 (range 2–4)) ($P < 0{\cdot}001$). *The median survival was 21·5 (range 4–62) weeks in the group receiving laser treatment, compared with 14·5 (range 7–102) weeks in the intubated group* ($P = 0{\cdot}09$). *The median inpatient stay as a proportion of survival time was 14 per cent in the group receiving laser treatment compared with 15 per cent in the intubated group* ($P > 0{\cdot}05$). *The median weight loss was less in the laser-treated patients (2·0 (range 2–8)* versus *3·0 (range 0–10) kg,* $P = 0{\cdot}04$). *These results indicate that laser recanalization provides better palliation of dysphagia than does intubation, but this is not reflected in an improvement in survival time.*

Oesophageal carcinoma occurs in approximately 350 new patients in the west of Scotland each year of whom 82 per cent will die within 1 year and 96 per cent within 5 years, according to statistics from the West of Scotland Cancer Surveillance Unit. Surgery and radiotherapy hold the only hope of cure but the long-term results are disappointing[1,2]. Chemotherapy alone has a poor response rate and considerable morbidity but may have a place in combination with other forms of treatment[3].

Intubation was first introduced[4] for the palliation of oesophageal tumours in the early 1880s and remains the method of palliation most commonly used today[5]. The development of endoscopic pulsion intubation has further reduced the complication rate associated with this technique[6–8]. Oesophageal tumours were first destroyed by thermal damage over 50 years ago[9], but it was not until the development of therapeutic lasers compatible with a flexible endoscope[10] that the technique could be carried out with sufficient safety to provide an acceptable alternative to intubation.

Several published studies have compared laser recanalization with other forms of treatment, most being retrospective non-randomized or using historical controls[11–15]. Only two prospective randomized studies have been undertaken: one compared laser therapy alone with intubation following laser recanalization[16], the other directly compared the two techniques[17]. Both studies concentrated on the initial palliation but it has been shown[18] that there is a deterioration in swallowing before death. The aim of the present study was to compare laser recanalization and endoscopic intubation in a randomized manner in the palliation of malignant dysphagia, following the patients until death.

Patients and methods

Forty consecutive patients with histologically confirmed circumferential malignant dysphagia who required palliative therapy were randomized to receive either laser recanalization or pulsion intubation. Those with recurrent disease after previous treatment were excluded. All patients were initially assessed and considered for resection Palliative treatment was given only if the patient was considered unlikely to survive resection, was found to have an irresectable tumour at surgery or had widespread metastasis. Randomization was performed using a random number sequence before endoscopy Patient details are shown in *Table 1*, there were no significant differences between the two groups.

All the endoscopies were carried out under sedation with diazepam or midazolam, with the addition of pethidine for analgesia as required The stricture was then dilated if necessary up to 18 mm, using either the Celestin (Medoc, Tetbury, UK) or Eder Puestow (Keymed, Southend-on-Sea, UK) dilators

Laser therapy

Laser treatment was given using a Fibrelase 100 neodymium yttrium–aluminium–garnet laser (Living Technology, Glasgow, UK), which has a wavelength of 1064 nm and a power range of 15–100 W. The beam was channelled down a flexible fibre, 0·4 mm in diameter, housed within a 2-mm Teflon (Du Pont, Stevenage, UK) sheath. A continuous stream of carbon dioxide was passed between the fibre and the Teflon casing. A brush-stroke technique was used as this has been found to maximize tumour tissue damage without undue fibre trauma Gaseous

Table 1 *Clinical features of 40 patients on presentation*

	Group receiving intubation ($n = 20$)	Group treated by laser ($n = 20$)
Age (years)*	69 (43–87)	78 (44–80)
Sex ratio (M F)	12.8	10·10
Histology		
Squamous cell carcinoma	7	13
Adenocarcinoma	13	7
Site		
Oesophageal	10	13
Oesophagogastric	10	7
Distance from incisors (cm)*	32 (25–39)	32 (20–38)
Duration of symptoms (months)*	4 (2–7)	4 (1–9)
Reason for palliation		
Metastatic disease	15	11
Unfit	5	9

*Values are median (range). No significant differences were found between the groups

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distension was prevented by using continuous suction through a nasogastric tube attached alongside the endoscope. Where possible, laser therapy began at the distal end of the tumour but in two patients dilatation proved impossible (because of failure to pass the guidewire) and in these the laser was used in an antegrade fashion, working from the proximal end distally until a channel was obtained.

Patients were electively readmitted at 3–6-week intervals, regardless of symptoms, for repeat endoscopy on an inpatient basis. Laser therapy was given to developing exophytic areas if required. The period between admissions was determined by the time from referral (a more intensive period of treatment is usually required initially) and the clinical or symptomatic response. The aim was to repeat endoscopy before any increase in dysphagia had occurred. If a patient developed recurrent dysphagia requiring more frequent endoscopic laser therapy because of rapid tumour growth, endoscopic intubation was carried out; intubation was also carried out in any patient who developed a tracheo-oesophageal fistula, as laser therapy is inappropriate in this situation. Following laser treatment the patients were advised to chew food thoroughly but were not restricted in diet. A chest radiograph was taken after laser therapy only if the procedure was technically difficult or if there was a clinical suspicion of perforation.

Endoscopic intubation

Patients randomized to intubation had a 10- or 15-cm Atkinson oesophageal prosthesis (Keymed) inserted. This tube has a large internal diameter of 13 mm. The position of the tube was checked endoscopically immediately after insertion. A penetrated chest radiograph was obtained immediately after intubation to check that perforation had not occurred. Patients were advised to eat as they wished and to chew food well, to take small mouthfuls and to drink carbonated fluids when they ate.

Patients were reviewed at the outpatient clinic at about 6-week intervals to assess weight and swallowing ability until this became inappropriate due to clinical deterioration. Those with recurrent dysphagia were readmitted urgently, reassessed endoscopically and appropriate treatment given.

One patient was randomized to intubation, but at initial endoscopy it proved impossible to pass the flexible guidewire to allow dilatation. This patient subsequently underwent recanalization by antegrade laser therapy and was followed up as described in the previous section. This patient has been included in the intubation group and analysed on an 'intention to treat' basis.

Patient assessment

All patients were referred for relief of dysphagia. Swallowing ability was graded on a simple numerical scale (*Table 2*) using the patient's subjective impression of dietary intake. Before treatment patients were asked to grade their swallowing using this scale, and this procedure was repeated whenever the patient was readmitted (laser-treated group) or when the patient returned to the outpatient clinic (intubated group). During the terminal phase of the illness the swallowing grade was obtained from the patient's relatives or hospital/hospice staff. The patient's weight was recorded at each hospital visit and as close to death as possible. Survival was recorded in weeks from the time of initial treatment.

Table 2 *Swallowing grade*

Grade	Symptoms
0	Absolute dysphagia
1	Able to swallow saliva and fluids with difficulty, requiring an intravenous infusion to maintain adequate fluid intake
2	Unable to manage any solids but swallowing liquids adequately
3	Difficulty with hard solids but able to manage semisolids
4	Able to eat anything

Statistical analysis

This study was intended as an assessment of clinical treatment and the results have been analysed on an 'intention to treat' basis. The significance of the observed differences was assessed using the Mann–Whitney *U* test and Fisher's exact test as appropriate.

Results

The effect of treatment on swallowing grade is shown in *Figure 1*. All but two laser-treated patients tolerated a normal diet at some time during their illness (median swallowing grade 4 (range 3–4)) and most intubated patients managed a semisolid diet with ease, but two patients only drank liquids (median grade 3 (range 2–4)) ($P < 0·001$). Before death swallowing was better in the laser-treated group (median grade 3 (range 2–4)) than in the intubated group (median grade 2·5 (range 0–4)) ($P = 0·01$).

Recurrent dysphagia occurred in one patient who received laser treatment and in four who underwent intubation. The patient in the laser-treated group developed external compression as a result of extraluminal tumour during terminal decline and was intubated with relief of dysphagia. Three patients in the intubated group developed food bolus obstruction on six occasions; on each occasion the tube was easily cleared endoscopically. In the fourth intubated patient recurrent dysphagia was caused by tumour overgrowth at the upper end of the tube, which was successfully cleared by laser vaporization, restoring patency of the Atkinson tube.

Weight loss during follow-up was less in the laser-treated group than in the intubated patients (median (range) 2·0 (2–8) *versus* 3·0 (0–10) kg, $P = 0·04$). Patients receiving laser treatment underwent 96 endoscopies: 79 with laser and dilatation; 11 with dilatation alone; one with dilatation and intubation; one intubation alone; and on four occasions no treatment was required. In the group that was intubated (including the patient who was randomized to intubation but actually received laser therapy), the patients required 37 endoscopies: 19 with dilatation and intubation; seven with dilatation and laser therapy; six for clearance of food bolus; two dilatations alone; two laser therapy alone; and on one occasion no treatment was required.

Survival from the time of diagnosis was measured in weeks. The patients treated by laser survived a median (range) of 21·5 (4–62) weeks compared with 14·5 (7–102) weeks in the intubated group ($P = 0·09$). The median (range) proportion

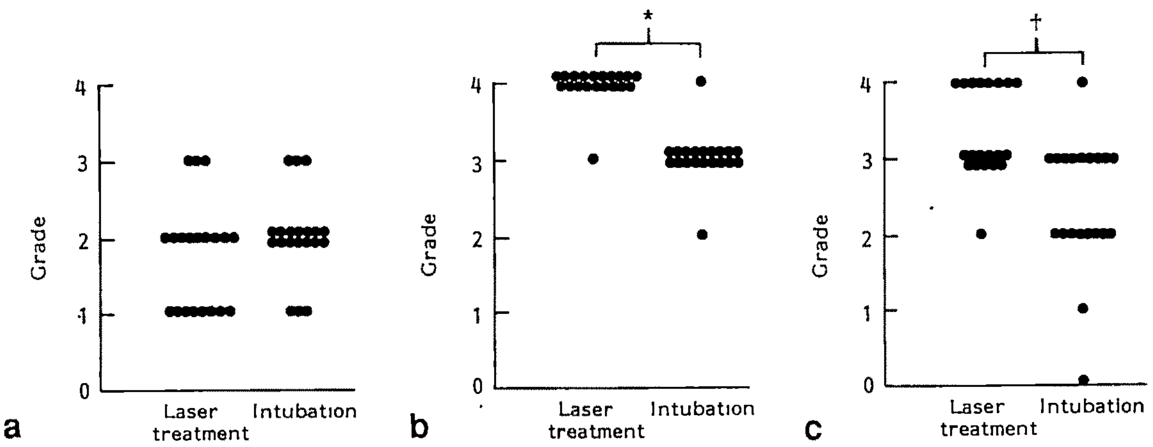

Figure 1 *Swallowing grade* **a** *at presentation,* **b** *after treatment and* **c** *before death* *$P < 0·001$, †$P = 0·01$ (*Mann–Whitney* U *test*)

of survival time spent as an inpatient was 14 (4–100) per cent in the laser-treated group and 15 (3–35) per cent in the intubated group ($P > 0.05$). The patients treated by laser required more admissions: median 5 (range 1–9) *versus* 2 (range 1–10) ($P = 0.001$).

Complications

One procedure-related death occurred in the group treated by laser: this patient developed a perforation during dilatation before the fourth laser session, 16 weeks after referral. The perforation was treated surgically but the patient died. Two other perforations occurred in the laser-treated group; both patients survived with conservative treatment. One further patient developed a tracheo-oesophageal fistula and was intubated to relieve respiratory symptoms. There was one case of aspiration pneumonia, which required admission; the patient recovered after treatment with antibiotics and physiotherapy.

No perforations or fistulas occurred in the patients who underwent intubation. One intubation failed, but the patient responded to subsequent laser recanalization. Three patients required a total of six admissions for obstruction due to a food bolus. There were four patients with significant aspiration pneumonia requiring admission, for terminal care in three. Secondary obstruction from tumour overgrowth occurred in one patient.

Dyspepsia due to gastro-oesophageal reflux was common in both groups. In all but two patients this was adequately controlled with antacids and H_2-receptor antagonists. Significant anorexia, which limited intake despite an adequate channel, carried a poor prognosis and often heralded the terminal decline.

Discussion

Since the first report in 1982 of laser recanalization of oesophageal tumours[19] most workers have concentrated on the technical feasibility of the procedure or on factors affecting outcome[20–27]. Comparative studies have generally been retrospective and have used small numbers of historical controls[11–15]. In the first of two randomized studies, Barr and colleagues[16] compared laser treatment with laser therapy followed by intubation. They used quality-of-life assessment (QL index and a linear analogue self-assessment scale) to evaluate the success of treatment. However, a nutritional diary was used to assess swallowing; we consider that the patients' impression of how they are eating is a better reflection of symptom relief than dietary intake. The resulting grade is probably an overestimate as patients tend to adjust their diet to avoid dysphagia. Any tendency to exaggerate the swallowing ability will occur in all patients and so should not affect the comparison of the two treatments.

Alderson and Wright[17] compared laser therapy and intubation, but they reported only the initial outcome, as their patients were not followed until death. They concluded that tumours <4 cm in length are best treated by laser therapy and that those longer than this are better managed by intubation. In our own experience[18] we have not found tumour length to have an independent influence on outcome, although longer tumours tend to be more time consuming and technically more difficult to treat. The findings of Alderson and Wright may be biased by the number of patients with short tumours who had local recurrence following surgery, as this has been found to be a subgroup that tends to do well with laser therapy, and may survive longer[18].

All 40 patients entered into this study swallowed better as a result of treatment. One patient randomized to intubation required laser recanalization when a guidewire could not be passed. Although in this study a lumen was achieved in all 21 patients who were treated with the laser, overall experience has shown that in approximately 4 per cent of patients recanalization is impossible for technical reasons. Another 4 per cent of patients with malignant dysphagia refuse to take food despite restoration of an adequate lumen[18]. Several authors have recognized that pretreatment anorexia rarely responds to recanalization[23,24,27] and that these patients are often in the terminal stages of illness. In the present study two intubated patients refused to swallow more than liquids because of this factor.

The surprising result of improved swallowing achieved by recanalization was the significant reduction in weight loss within this group. This difference was significant at the 5 per cent level and supports the belief that the subjective improvement in swallowing may be associated with better nutritional intake.

Both treatments are associated with significant complications. The perforations noted in this study do not reflect significant differences between the techniques because of the small numbers. The authors' overall perforation rate in laser-treated patients is 6·4 per cent[18], compared with 7 per cent for pulsion intubation over the past 5 years. The only death associated with laser treatment occurred after operation following a perforation. Patients with oesophageal perforation are now managed conservatively, which in our experience is successful in up to 80 per cent of cases[18,28].

Early reports on laser recanalization suggested that laser therapy could provide adequate palliation in all patients[11,26,27,29]. Experience in the treatment of malignant dysphagia with the laser has shown that this is not the case, and that some patients may be better treated with intubation or a combination of laser therapy and intubation. The decision of which treatment to employ needs to take into account both medical and social factors: a patient who lives some distance from a laser centre may be more appropriately treated by intubation to avoid the need for regular admission; laser therapy is inappropriate in the presence of a tracheo-oesophageal fistula or when extrinsic compression is the main factor causing dysphagia; intubation is impossible if a guidewire cannot be passed and migration of the tube is common if the lesion is not circumferential. It has been suggested that long tumours are best treated by intubation. In patients with such tumours it takes more time to achieve recanalization but it has been found that length does not affect the ability of the laser to restore swallowing[18].

In the present study both methods relieved symptoms. Palliation was significantly better after laser recanalization in terms of swallowing ability and weight loss, but there was no improvement in survival. We have come to view these treatments as complementary and they may safely be combined in the same patient[30]. Problems can occur due to progression of disease or as a complication of the treatment. The appropriately timed application of each method can improve the standard of palliation.

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Case report

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High jejunal obstruction: a complication of percutaneous endoscopic gastrostomy

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Since its inception[1] in 1980, percutaneous endoscopic gastrostomy has become a widely used technique for the provision of long-term nutritional support. For the experienced endoscopist, the technique is relatively simple and is usually associated with low morbidity and mortality rates[2]. A complication of percutaneous endoscopic gastrostomy that highlights the necessity for correct placement of the feeding tube is reported.

Case report

A 9-year-old girl had been born with multiple neurological problems including dysphagia. Percutaneous endoscopic gastrostomy was performed at another centre 2 months before an acute admission with abdominal pain and vomiting Symptoms were related to use of the feeding tube. The internal retention disc was located endoscopically in the duodenum and successfully withdrawn to its original position 2 cm from the pylorus. Migration of the tube was assumed to be caused by loosening of the retention discs. The patient reattended 3 weeks later in identical fashion, and per-tube contrast studies (*Figure 1*) demonstrated a proximal jejunal obstruction caused by distal migration of the tube and lodging of the internal retention disc in the proximal jejunum. Once again the tube was successfully retrieved and removed endoscopically. A new gastrostomy tube was sited in the body of the stomach.

Discussion

The benefits of percutaneous endoscopic gastrostomy are well documented[3,4] While problematic tube migration has been previously described, it has been exclusive to the older Foley catheter type of feeding tubes[5], the large balloons of which lodged in or around the pylorus. The small diameter (2·5 cm) of the internal retention disc of the Freka (Fresnius, Runcorn, UK) percutaneous endoscopic gastrostomy system allows it to migrate further along the gastrointestinal tract.

The cause of the tube migration is debatable. It was originally assumed that the tube became dislodged from incorrect handling. However, despite subsequent advice and meticulous handling, the tube migrated again. Detailed examination of the tube after removal did not reveal any manufacturing faults that might predispose to migration. Since resiting the tube 6 months ago the patient has experienced no further problems It is therefore assumed that the original positioning of the tube was too close to the pylorus and that the peristaltic activity at the antrum precipitated its migration.

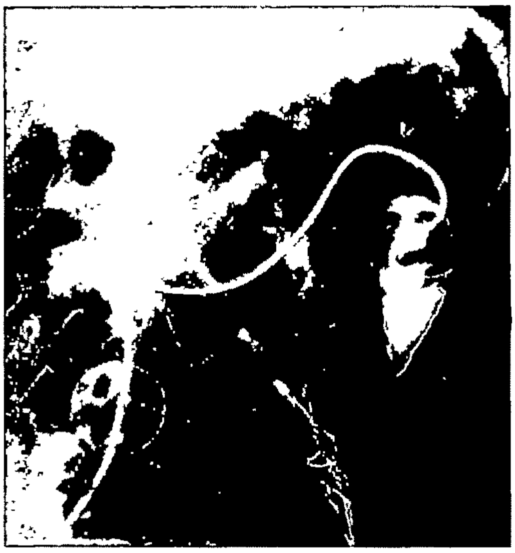

Figure 1 *Per-gastrostomy tube contrast study confirming internal retention disc in the proximal jejunum*

This case illustrates the necessity for correct positioning of the percutaneous endoscopic gastrostomy tube away from the pyloric antrum, as the complications of small bowel obstruction in an already frail patient are potentially disastrous.

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Closure of laparotomy wounds: skin staples *versus* sutures

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To investigate the routine use of a skin stapling device for the closure of midline abdominal wounds, 48 patients were randomized to receive skin staples or subcuticular polydioxanone sutures. The mean (range) time for closure with staples was 8·0 (3·4–14·8) s cm^{-1} while subcuticular closure took 12·7 (9·6–28·0) s cm^{-1}. The mean time saved per patient with skin staples was 77 s. Wound pain and requirements for analgesia were significantly lower in the sutured group. The mean cost per patient was £1·41 for subcuticular closure and £7·72 for stapling; the latter also incurred an additional cost of £6·27 for staple removal. No clear benefit derives from the use of staples in the closure of abdominal wounds.

Any method of skin closure should provide adequate approximation of the tissues to allow wound healing with minimal risk of infection and should produce an acceptable cosmetic result. The method should be simple and quick to use, and should be economical.

Automatic skin staplers were first introduced in 1972 as a development from early Russian tissue-stapling devices[1]. They are said to save considerable amounts of operating time[2–4]. This has led to a steady growth in use of such staplers, their sizeable cost being justified by the resources saved.

Subcuticular skin closure is an acceptable method for skin approximation in most types of surgery and can be quickly performed. Clinical experience has suggested that time saving using staples is not significant and their use associated with more discomfort.

A prospective randomized trial was therefore undertaken to compare continuous subcuticular sutures with stapled skin closure.

Patients and methods

A total of 48 patients (22 men, 26 women; age 27–89 (mean 65) years) undergoing laparotomy through a midline incision were randomized to skin closure using an automatic skin stapling device (Weck, Swindon, UK) or continuous subcuticular undyed 3/0 polydioxanone (PDS; Ethicon, Edinburgh, UK). All wounds were made and closed by a single operator with more than 1 year's experience of both methods. 0 PDS was used for abdominal wall approximation using a standard mass closure technique. No fat stitch was used and all wounds were treated with dry povidone–iodine spray before skin closure For stapled wounds the size of the stapler was chosen by the scrub nurse using judgement on the number of staples required to close the wound

The time taken for skin approximation was measured by an independent observer from the time that the closure device was picked up to the time at which the wound was closed and the device put down If a further stapler was required to complete wound closure, the additional time taken was included

No knots were used for the subcuticular suture, the stitch being passed back and forth beneath the skin twice before and after wound suturing. The ends of the suture were trimmed flush with the skin after the wound had been cleaned and dried, the material being left to be absorbed. Both types of wound were covered with self-adhesive dressings.

The 100-mm visual analogue pain scale has been shown to give an accurate measure of pain that is both reliable and reproducible[5,6]. For each patient at 5 days after operation, or at hospital discharge if sooner, a standard 100-mm analogue pain scale test was performed to assess discomfort from the wound All patients received continuous intravenous infusion of opiate for the first 48 h after surgery. The total number of additional opiate and non-opiate analgesic doses was recorded for the first 10 days (removal of clips) On the fifth day the lengths of the wounds were measured. At 1 month after surgery an experienced observer, unaware of the closure technique, graded wounds on a five-point scale for appearance The patient's opinion was also determined by the observer using the same scale.

Statistical analysis was carried out using the Mann–Whitney *U* test.

Results

Twenty-two patients received stapled skin closure and 26 subcuticular PDS. No significant difference existed between the two groups for age, sex, body mass index, length of wound, or duration or type of operation (*Table 1*).

Wound closure

The groups were evenly matched for wound length ($z=0{\cdot}11$, $P>0{\cdot}9$). The mean closure time for the stapled group was 147 s; it was 224 s for those receiving PDS sutures. A mean of 25 (range 13–46) staples were needed to close each wound with up to 15 (mean 6) being wasted in each case.

The rate of wound closure was calculated for each patient from the wound length and the total closure time. For the stapled group the mean (range) rate was 8·0 (3·4–14·8) s cm^{-1} and in the subcuticular group 12·7 (9·6–28 0) s cm^{-1}. Four stapled wounds required two staplers; the closure rate for these patients was between 8·3 and 9·6 s cm^{-1}. The difference in closure rate between the two groups was highly significant ($z=3{\cdot}75$, $P<0\ 0002$).

Postoperative pain and wounds

For those patients in whom PDS was used the median pain score was 16 mm. Patients whose wounds were closed with staples had a median score of 28 mm. The difference in postoperative discomfort measured at 5 days (*Table 2*) was significant ($z=2{\cdot}22$, $P=0{\cdot}03$). The group receiving PDS closure needed significantly less opiate and non-opiate analgesia than those undergoing stapling (*Table 2*).

One wound infection with the discharge of pus occurred in each group. Objective assessment of the wounds at 1 month revealed no significant difference in assessment by the independent observer or patient (*Table 2*) No late hypertrophic reaction has been observed after 1 year in either group.

Table 1 *Comparison of patient groups*

	Staples ($n=22$)	Polydioxanone ($n=26$)
Age (years)*	66 (38–89)	64 (27–80)
Sex ratio (M·F)	10 12	12.14
Body mass index (kg m^{-2})*	52 1 (37·3–70·6)	50 9 (41 2–78 6)
Wound length (cm)*	18 4 (13–27)	18·5 (10–28)
Operation time (min)*	88 (12–210)	91 (20–190)
Operation		
Upper abdomen	10	10
Lower abdomen	12	16

* Values are mean (range). Differences between groups were not significant

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Table 2 *Postoperative pain, requirement for additional analgesia and appearance of wounds*

	Staples ($n = 22$)	Polydioxanone ($n = 26$)	P*
Pain score (mm)	31·9 (15–50)	25·1 (1–73)	0·03
Median	28	16	
Additional opiate analgesia (doses)	4·3 (0–13)	2·0 (0–10)	0·03
Additional non-opiate analgesia (doses)	6·5 (0–14)	4·7 (0–19)	0·05
Wound appearance score	4·1	3·6	n.s.

Values are mean (range). * Mann–Whitney *U* test; n.s., not significant

Costs

Only one length of PDS was needed per patient, at a cost of £1·41 per packet. Four patients required additional staplers to achieve wound closure, giving a mean cost of £7·72. No additional costs, other than for a change of dressing, were incurred by patients receiving PDS closure. For those with stapled wounds, a staple remover, basic dressing pack and nursing time (inpatient or district nursing service) were required for the removal of staples. The mean estimated cost was £6·27 per patient.

Discussion

Subcuticular wound closure provides good skin approximation, with rates of infection no higher than those reported for interrupted sutures, even in contaminated wounds[7]. PDS elicits a minimal tissue reaction, has a predictable reabsorption pattern[8] and, when used as a subcuticular closure material, is associated with a low rate of wound infection[9].

Skin staples are associated with low wound infection rates that are better than those of conventional percutaneous sutures[10–12]. They are reported to save operating time, especially when compared with interrupted sutures, showing savings of up to 5 min 20 s per laparotomy wound[2–4]. Smaller time savings occur when staples are compared with subcuticular closure[8,13]. This study confirms these findings, although the mean saving with staples of only 77 s per wound is the smallest reported. The chance of including another case on the list because of time saved is unrealistic with such small differences, while the use of automatic skin staplers in moderate-sized wounds on the basis of time savings alone is hard to support.

Stapled wound closure costs £12·58 more per wound than closure by PDS. At the rate of stapler usage described, the 2504 staplers employed by East Dorset Health District during the year of the study would have been used to close 2053 wounds (18 per cent of wounds required more than one stapler). This represents an additional annual cost above subcuticular skin closure with PDS of over £25 000.

If stapled closure is associated with fewer wound complications than subcuticular PDS then an additional cost may justify other savings. No evidence for this effect exists.

No account has been taken within the calculations of the additional cost incurred from the higher analgesia requirements for patients with stapled wounds. The total number of analgesia doses required by a patient is a less effective means of comparison but in this study provided a guide to the additional resources required by the stapled group of patients. The finding of increased wound pain and analgesia requirements within this group is at variance with results of other workers[4,14]. In these reports, however, the staples were compared with conventional interrupted sutures, which may explain the different findings. Other types of skin stapler with different staple configurations may evoke less postoperative pain. No comparative study has addressed this issue.

Subcuticular PDS has been shown to give a better cosmetic result within the first 6 months than simple sutures or skin staples[15]. Conventionally closed wounds are stronger[16] than those closed with staples at 21 days, and are under less tension[17]. In the context of skin flap procedures a much greater proportion of flap necrosis has been found with staples[17]. The comparison of wound appearance in this study has not shown an early advantage over subcuticular closure. This study demonstrates no significant advantage in the use of staples over subcuticular PDS in the closure of midline laparotomy wounds.

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Evaluation of routine upper digestive tract endoscopy before laparoscopic cholecystectomy

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Endoscopy of the upper digestive tract was performed in 376 patients with symptomatic gallstone disease before elective laparoscopic cholecystectomy. Abnormalities were found in 60 patients (16·0 per cent); these included peptic ulcer (n = *14*), *gastric erosions* (n = *15*) *and oesophagitis* (n = *11*). *Thirty patients were treated medically and two by endoscopic polypectomy. In four patients endoscopy led to cancellation of cholecystectomy; in two the complaints have persisted. Statistical analysis of 28 variables showed few significant differences in symptoms between patients with normal and those with abnormal appearances at endoscopy. It is concluded that routine endoscopy before laparoscopic cholecystectomy is neither clinically useful nor cost effective in patients with symptomatic gallstone disease. This conclusion is related exclusively to patients with typical gallstone symptoms according to the definition used in this department.*

The identification of symptoms specific for gallstones has been the aim of numerous studies[1–5]. Nevertheless, 'to date, it has never been established which symptoms are specifically caused by stones in the gallbladder'[6] Endoscopic abnormalities of the upper digestive tract have been reported in up to 44 per cent of patients with so-called symptomatic gallstone disease[7,8]. It is not known to what extent these abnormalities may cause symptoms themselves, or may be the cause of the complaints before or after operation in some patients with gallstones. For these reasons routine endoscopy of the upper digestive tract before elective cholecystectomy has been advised[8].

One of the main benefits of laparoscopic cholecystectomy is improved comfort of the patient in the postoperative period[9–11] Because endoscopy of the upper digestive tract is uncomfortable, patients ask about its benefit. The purpose of this study was to evaluate this benefit, and in particular to determine the prevalence of abnormal findings at endoscopy in patients before elective laparoscopic cholecystectomy, and the role of the investigation in determining treatment. In addition, attempts were made to assess to what extent symptoms predicted the presence of abnormalities in the upper gastrointestinal tract.

Patients and methods

A total of 533 patients were admitted for elective laparoscopic cholecystectomy between October 1990 and March 1991. All underwent endoscopy of the upper digestive tract before cholecystectomy In 153 patients the investigation had been performed by the family doctor within 3 months before admission and was reported to be normal. Consequently endoscopy was not repeated and these patients were excluded from the study Of the 380 patients in whom endoscopy was performed, four did not tolerate the procedure, leaving 376 for analysis

Symptomatic gallstone disease was diagnosed clinically in the presence of the following symptoms for more than 4 weeks[11]· severe attacks of pain or colic, usually in the epigastrium and right upper abdomen, pain radiating to the back and right shoulder, and pain or other gastrointestinal symptoms provoked by food or stress In addition, some patients who had symptoms not entirely typical of gallstone disease also underwent cholecystectomy and were included in the study

The severity of symptoms was graded on a scale[2] from 0 to 3 Patients with specific symptoms of essential dyspepsia were identified using the score of Talley *et al.*[4] and those with a score of 60 points or more excluded Tenderness of the right upper abdomen and abnormal laboratory findings were not present in every case.

All patients underwent real-time ultrasonography using a 5-MHz probe (Sonoline AC, Siemens, Erlangen, Germany) Gallstones, polyps, an empty gallbladder or non-visualization of the gallbladder were defined by the criteria of Jorgensen[12]. All patients had some abnormality on ultrasonography

Endoscopy of the oesophagus, stomach and duodenum was carried out using forward-viewing instruments and simultaneous video-recording (Olympus GIF100 and OTV-F2; Olympus, Hamburg, Germany). Before endoscopy, atropine sulphate 0·5 mg, *N*-butyl-scopolamine bromide 60 mg and midazolam 2·5–5 mg were given intravenously All endoscopic findings were recorded prospectively on a computer database.

Endoscopic findings were classified as: normal (including type I hiatus hernia without oesophagitis); oesophagitis[13] grades 1–3; gastric erosions[14], ulcer disease[15], polyps or polypoid structures, scars or deformities of the duodenal bulb[16]; and diverticula of the duodenum

A self-administered questionnaire covering 68 variables was given to every patient before endoscopy. Twenty-eight of these, selected after study of publications on symptoms in gallstone disease[2,4,5], were analysed in detail. Attacks of pain were not differentiated from colic. Instead, pain was evaluated for localization, radiation, duration, and intensity Alcohol consumption and smoking were noted Obesity was defined as body-weight > 10 per cent above normal (normal weight in kilograms was defined for men as height in centimetres minus 100 and for women as 90 per cent of height in centimetres minus 100).

Statistical analysis

Data were analysed by the biomedical data package PC-90 (BMDP Statistical Software, Cork, Ireland) Univariate analysis was carried out using the Wilcoxon rank sum test and χ^2 test with Yates' correction as appropriate. $P < 0·05$ was accepted as significant. Regression tree analysis was performed to discriminate between the group of patients with inflammatory diseases of the upper intestinal tract (ulcers, erosions or oesophagitis) and those with normal findings (Knowledge Seeker software, version 2.07, First Mark Technologies, Ottawa, Canada). This analysis takes missing values into consideration

Results

The median age of the 376 patients was 51 (range 18–87) years, the female:male ratio 282:94 (3:1), the median weight 70 (range 41–148) kg and the median height 168 (range 148–193) cm. Severity of symptoms[2] was graded for 50 patients as grade 0, for 205 as grade 1, for 117 as grade 2 and for four as grade 3. The 50 patients with grade 0 were, however, not symptom-free; they had symptoms different from typical gallstone symptoms according to our definition[11]. This number includes patients with polyps of the gallbladder, those awaiting transplantation

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Table 1 *Endoscopic findings in the upper digestive tract in 376 patients before laparoscopic cholecystectomy*

Diagnosis	No.	Additional treatment
Gastric erosions	15 (4·0)	15
Peptic ulcer	14 (3·7)	14
Oesophagitis	11 (2·9)	1
Scars	9 (2·4)	0
Polyps	8 (2·1)	2
Duodenal diverticula	1	0
Oesophageal stenosis	1	0
Type II hiatal hernia	1	0
Abnormal findings	60 (16·0)	32 (8·5)

Values in parentheses are percentages

Table 2 *Analysis of history, symptoms and covariables in 316 patients with normal endoscopic findings before laparoscopic cholecystectomy*

Age (years)*	49·9
Sex ratio (M:F)	24·1:75·9
Time since diagnosis of gallstones (months)*	46·9
Obesity (percentage over normal weight)*	10·2
Weight loss in past 3 months (kg)*	1·1
Pain	82·9
Time since first occurrence (months)*	38·9
Time since last attack (months)*	2·4
Duration of attacks	
<30 min	13·6
30 min–6 h	51·6
>6 h	25·9
Not identified	9·9
Location	
Right upper abdomen	59·2
Epigastrium	13·9
All over upper abdomen	23·4
Before meals	22·1
After meals	72·2
Improvement after meals or milk	14·6
Intensity on visual analogue scale (0–100)*	41·0
Other symptoms	
Feeling of abdominal pressure	86·9
Bloating	71·2
Nausea	59·5
Vomiting	35·8
Loss of appetite	38·0
Early satiation	71·5
Avoidance of food in general	84·8
Intolerance of fatty meals	69·9
Restricted diet because of abdominal symptoms	41·5
Lifestyle	
Alcohol consumption	5·4
Smoking	22·2
Time off work because of abdominal symptoms (months)*	1·1

*Values are medians; all other values are percentages

and those who travelled frequently and were afraid of unexpected complications. Previous treatments included analgesic drugs ($n=188$), drugs to dissolve the stones ($n=30$), papillotomy ($n=5$), lithotripsy ($n=6$) and others ($n=19$). A total of 128 patients (34·0 per cent) did not report any previous treatment.

There were no complications of gastroscopy. No abnormalities were found in 316 patients (84·0 per cent) including 80 (21·3 per cent) with type I hiatal hernia without oesophagitis. Altogether, 60 patients (16·0 per cent) had abnormal findings (*Table 1*).

The most common finding was gastric erosions, present in 15 patients (4·0 per cent). All patients with erosions were treated with omeprazole and colloidal bismuth subcitrate orally. In one patient the erosions were so extensive that cholecystectomy was not performed. This patient is still being treated by diet for abdominal symptoms but is free of pain. All other patients with erosions underwent cholecystectomy.

Fourteen patients (3·7 per cent) had peptic ulcers, gastric in eight and duodenal in six; none of these ulcers had been suspected previously. All were treated with omeprazole and colloidal bismuth subcitrate orally. Nine of these patients had typical gallbladder symptoms and underwent cholecystectomy after histological confirmation that their ulcers were benign. Three patients with gastric and two with duodenal ulcers were not operated on because of atypical symptoms of gallbladder disease. Persisting abdominal symptoms after the gastric ulcer had healed led to cholecystectomy in two patients 8 and 12 months later. Both are now symptom-free.

Eleven patients (2·9 per cent) had oesophagitis, grade 1 in ten and grade 2 in one. The latter patient was treated with cisapride orally. Scars or deformities without inflammation were present in nine patients (2·4 per cent), four in the antrum or pylorus and five in the duodenal bulb. Eight patients (2·1 per cent) had polyps, seven in the stomach and one in the duodenum. Two large polyps were removed endoscopically, one from the cardia (histological examination showed a villous adenoma) and one from the duodenum (tubular adenoma). Other abnormalities comprised duodenal diverticula ($n=1$), a small benign stenosis of the oesophagus ($n=1$) and a type II hiatal hernia ($n=1$).

Endoscopy resulted in additional treatment for 32 patients (8·5 per cent). These included 15 with gastric erosions, 14 with gastroduodenal ulcers and one with grade 2 oesophagitis; all received medical treatment. Endoscopic polypectomy was carried out in two patients. Of the six who were not operated on immediately, two underwent surgery later for persisting symptoms.

Only four patients (1·1 per cent) did not undergo cholecystectomy because of endoscopic findings: three who had ulcers and one with gastric erosions. One patient with a duodenal ulcer and one with extensive gastric erosions still have symptoms but have declined cholecystectomy.

The distribution of the 28 predefined variables in patients with normal endoscopic findings is shown on *Table 2*. The most common were a feeling of abdominal pressure (86·9 per cent), abdominal pain (82·9 per cent) and unwillingness to eat (84·8 per cent). On univariate analysis there were no significant differences in the intensity of pain as assessed by a visual analogue scale between patients with ulcers, erosions, oesophagitis, scars or polyps and those with normal endoscopic findings. Pain was present after meals significantly less often in patients with gastric erosions ($P=0·014$). Obesity was more common among patients with gastric erosions ($P=0·035$) and the time since the last attack of pain was longer in those with oesophagitis ($P=0·002$). No significant differences were found for variables of patients with peptic ulcers, scars or polyps. The group of patients with inflammatory diseases (including ulcers, erosions and oesophagitis) had pain over the whole upper abdomen less often ($P=0·033$) and less pain after meals ($P=0·033$) than those with normal endoscopic findings. As the positive predictive values of all variables were weak (1–9 per cent) it was not possible to identify patients with specific lesions by a single variable.

Regression tree analysis was performed to compare patients with peptic ulcer, erosion or oesophagitis and those with normal appearances. The combination of weight loss during the past 3 months and age showed a significant difference. Among patients whose loss of weight was <1·5 kg and who were aged under 45 years ($n=72$), the prevalence of inflammatory disease was only 2·8 per cent, whereas in those over 72 years old with weight loss <1·5 kg ($n=21$) it was 28·6 per cent. The prevalence among all 376 patients was 10·6 per cent. If endoscopy had been performed only in the group of patients over 72 years old with weight loss <1·5 kg, not more than 15 per cent of all lesions would have been found. There was no other significant combination of variables.

Discussion

The reported incidence of abnormal endoscopic findings in patients with gallstones varies from 6 to 44 per cent (*Table 3*). The numbers differ mainly because some authors classified type I hiatus hernia as an abnormal finding. The reported percentages of patients with ulcers, erosive gastritis, oesophagitis, scars and polyps are similar to the findings in the present study. No carcinomas were found in this series in contrast to that of Rassek *et al.*[8], who found one oesophageal and four gastric cancers among 589 endoscopies before elective cholecystectomy. These authors, however, included patients with all kinds of upper abdominal symptoms, even if these were not typical of gallbladder disease.

Few studies have dealt with the prevalence of upper gastrointestinal lesions in symptom-free volunteers (*Table 4*)[18–20]. Akdamar *et al.*[18] found that 38 per cent of 355 symptom-free subjects had abnormal endoscopic findings Johnsen *et al.*[20] reported endoscopic and histological findings in 619 subjects with and without dyspepsia; of 310 controls without symptoms or a history of abdominal disease, 4 per cent had peptic ulcer disease and 8 per cent oesophagitis of grade 1 or 2. The authors found 'some abnormality' of the upper digestive tract in 90 per cent of individuals. Ihamäki *et al.*[19] studied the relatives of patients with gastric carcinoma and 358 controls in Finland by endoscopy and gastric biopsy. The prevalence of peptic ulcer disease was 2 per cent and of histologically confirmed gastritis 59 per cent. The question 'What is a normal gastrointestinal tract?' remains to be answered[21]. The histological and clinical definitions of abnormality used in these studies differed from ours. In addition, these authors did not exclude the presence of gallstones by ultrasonography. The prevalence of gastroduodenal ulcer disease, erosive gastritis and oesophagitis, however, were similar to those in the present series. We conclude that subjects with typical gallstone symptoms and gallstones have the same prevalence of upper gastrointestinal lesions as those who are symptom-free.

The reported proportion of patients in whom the planned treatment had to be changed or extended because of endoscopic findings varies[7,8] from 1 to 12 per cent. In the present series the figure is 8·5 per cent. It is not known what would have happened to these patients had the endoscopic abnormalities not been detected and treated. Follow-up data have not been used to evaluate the benefit of routine endoscopy as it is not known which treatment influenced the outcome.

There were only four patients who did not undergo surgery because of endoscopic findings. Two still have complaints but have refused cholecystectomy; the other two are symptom-free and are the only patients of the 376 who can be said to have benefited from endoscopy. Rassek *et al.*[8] concluded that routine endoscopy of the upper gastrointestinal tract should be performed for all patients with symptomatic gallstone disease. Coleman *et al.*[7] reported abnormalities in 22 of 100 patients who had undergone endoscopy, but in only one did the endoscopic finding (duodenal ulceration) result in an additional operation. The authors suggested that endoscopy should be used selectively depending on symptoms rather than as a routine procedure, but did not state which symptoms these should be. The same conclusion was drawn by Labayle *et al.*[17], who found eight ulcers and one oesophageal carcinoma in 162 patients before cholecystectomy. Of 48 patients without typical gallstone symptoms, 13 per cent had endoscopic abnormalities compared with only 2 per cent of 114 with typical symptoms.

Patients with dyspepsia, ulcer disease and gallstone disease can be differentiated by their symptoms[4,22]. Talley *et al.*[4] found that a diagnosis of cholelithiasis was more likely than one of dyspepsia of unknown cause or peptic ulceration if: pain was more severe and not localized to the epigastrium alone; food, milk or antacids did not relieve pain; and pain was not present before meals. In the present series there were only a few variables for which there were significant differences between patients with normal and those with abnormal endoscopic findings. The fact that the analysis in this series included 28 variables for six groups of diagnoses increases considerably the likelihood of finding purely by chance a difference at $P<0\cdot05$. The reported differences should, therefore, not be overemphasized. The predictive values of these variables were too small to identify certain lesions. By regression tree analysis patients over the age of 72 years with loss of weight of $<1\cdot5$ kg were shown to have a higher risk (28·6 per cent) of ulcers, erosions or oesophagitis compared with all patients. This statistically significant result was, however, of no practical benefit. Endoscopy confined to this group of patients would diagnose only 15 per cent of all lesions, and almost all patients with endoscopic lesions required cholecystectomy after treatment of the luminal pathology.

Bates *et al.*[23] found that 42 per cent of 274 patients reported flatulence, 42 per cent indigestion and 27 per cent persistent pain 2 years after cholecystectomy, but only 35 of these patients had these symptoms investigated. The final diagnosis was gastritis or peptic ulceration in three patients and hiatus hernia in two. Ros and Zambon[24] reported that 47 per cent of 93 patients had persistent dyspepsia 2 years after cholecystectomy. Bodvall and Övergaard[25] found that 29 per cent of 1930 patients had some degree of pain and 11 per cent dyspepsia. In neither study was endoscopy performed. The results of the present study indicate that lesions of the upper gastrointestinal tract do not influence the symptoms of most patients with symptomatic gallstones. This is probably also true of patients after cholecystectomy, although this has yet to be proven.

It is concluded that patients with what is considered in this

Table 3 *Endoscopic findings in the literature in patients with gallstone disease*

Reference	No. of patients	Ulcer (%)	Gastric erosions (%)	Oesophagitis (%)	Scars (%)	Polyps (%)	Neoplasm (%)	Total (%)
Labayle *et al.*[17]	162	5	n a	n a	n a	n.a.	1	6
Coleman *et al.*[7]	100	4	3	2	n.a.	4	—	22
Rassek *et al.*[8]	589	6	3	2	2	4	5	44
Present study	376	4	4	3	2	2	—	16

n.a., No information available

Table 4 *Upper gastrointestinal endoscopy findings in the literature in a symptom-free normal population*

Reference	No. of patients	Ulcer (%)	Gastric erosions (%)	Oesophagitis (%)	Total abnormal (%)
Akdamar *et al.*[18]	355	4	12	9	38
Ihamäki *et al.*[19]	358	2	3	n.a.	12
Johnsen *et al.*[20]	310	4	n a.	8	90

n.a , No information available

department as 'typical gallstone symptoms' have the same prevalence of coexisting lesions of the upper digestive tract as symptom-free normal subjects. Patients with abnormal endoscopic findings cannot be differentiated by their symptoms from those with normal results. There are no reports of an increased risk of gastric carcinoma in patients with typical gallstone symptoms. If the prevalence of gastric carcinoma in these patients is the same as in the population as a whole, the chance of finding a gastric carcinoma by routine endoscopy[26,27] is between 1 in 3000 and 1 in 10 000. However, not every patient with carcinoma of the stomach or oesophagus can gain from the diagnosis as any benefit depends on the stage of the disease. The overall frequency of complications of endoscopy such as bleeding, perforation or cardiopulmonary problems is reported to be 0·1 per cent[28] and has to be taken into account. As patient comfort is one of the main benefits of laparoscopic cholecystectomy, and endoscopy of the upper digestive tract is an uncomfortable procedure, the latter should be shown to be of benefit before it can be recommended for routine use. In this study clear benefit was shown for only two of 376 patients. As a result it is concluded that routine endoscopy of the upper digestive tract before laparoscopic cholecystectomy is of no clinical benefit.

We do not recommend routine endoscopy before laparoscopic cholecystectomy. Endoscopy should be reserved for patients with persistent complaints after cholecystectomy. This recommendation applies only to patients who have been interviewed thoroughly and who are considered to have typical gallbladder symptoms.

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Laparoscopic cholangiography: a simple inexpensive technique using readily available materials

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Experience of laparoscopic cholecystectomy has increased rapidly since the operation was first performed in France in 1987; approximately 20 000 operations have been performed in the USA alone[1]. Laparoscopic cholecystectomy is now the treatment of choice for patients with symptomatic gallstones[2]. Opinion is, however, divided as to the need for routine peroperative cholangiography[3]. Even when a selective policy is adopted, cholangiography will be necessary in certain cases, particularly when ductal anatomy is unclear or common bile duct (CBD) stones are predicted. Unexpected CBD stones can be anticipated in 4–10 per cent of cases[4].

A number of specially designed cholangiography catheters and clamps are available for use in laparoscopic cholecystectomy, but they are expensive and not always readily available. For laparoscopic cholangiography in this unit, two simple inexpensive pieces of equipment that should be available in any operating theatre are used.

Surgical technique

The cystic duct is cleared of fat from its junction with the gallbladder to that with the common hepatic duct. A clip is placed on the gallbladder side of the cystic duct and the latter is opened with microscissors. A 14-Fr Abbocath cannula (Abbott Laboratories, Queenborough, Kent, UK) is inserted percutaneously under direct vision into the abdomen in the right upper quadrant just below the costal margin. The needle is withdrawn and a 4-Fr olive-tipped ureteric catheter (Porges; Uroplast, Windsor, UK) with its steel stylet in place is inserted through the cannula into the abdomen. The lower end of the cannula is gently held with a grasping forceps and guided to the hole in the cystic duct. Once over this hole the ureteric catheter can be manoeuvred easily into the duct (*Figure 1*). The stylet on the catheter aids passage through the spiral valve of Heister. The stylet is withdrawn, and the ureteric catheter is held in place by a second clip applied just firmly enough to stop it slipping out, but not so tightly as to cause occlusion. A 20-ml syringe filled with saline is attached to the catheter, and the cystic duct and CBD are flushed with saline. Radiological contrast is then injected under image intensification control. Once satisfactory cholangiograms have been obtained, the clip securing the ureteric catheter is removed and the catheter is withdrawn. Two clips are placed on the bile duct side of the hole in the cystic duct, and the latter is divided with microscissors.

Results

A total of 58 peroperative cholangiograms have been performed using this technique during 180 laparoscopic cholecystectomies. Success was obtained in 51 cases (88 per cent). Failure to obtain a satisfactory cholangiogram was caused by extravasation of contrast (three patients) and failure to negotiate the spiral valve (three). In a further case the tip of the ureteric catheter was found on screening to be in the duodenum and fell out of the cystic duct on withdrawal; the procedure was not repeated.

Peroperative cholangiography was normal in 43 of 51 cases. CBD stones were detected in seven patients and were dealt with by postoperative endoscopic sphincterotomy and stone extraction. A further patient had abnormal ductal anatomy.

Discussion

Although not all surgeons practise routine peroperative cholangiography during open cholecystectomy, we feel that it is desirable to do so in the laparoscopic operation, particularly early in the surgeon's experience when orientation and identification of the anatomy in Calot's triangle may not be entirely clear.

In spite of not being specifically designed for cholangiography, ureteric catheters have been used by many surgeons for cholangiography during open cholecystectomy and have been found satisfactory for the purpose. A 4-Fr ureteric catheter fits snugly into a 14-Fr Abbocath cannula, and no problems have been experienced with loss of carbon dioxide. Both items are readily available and are much cheaper than the catheters and clamps that have been specifically designed for peroperative cholangiography.

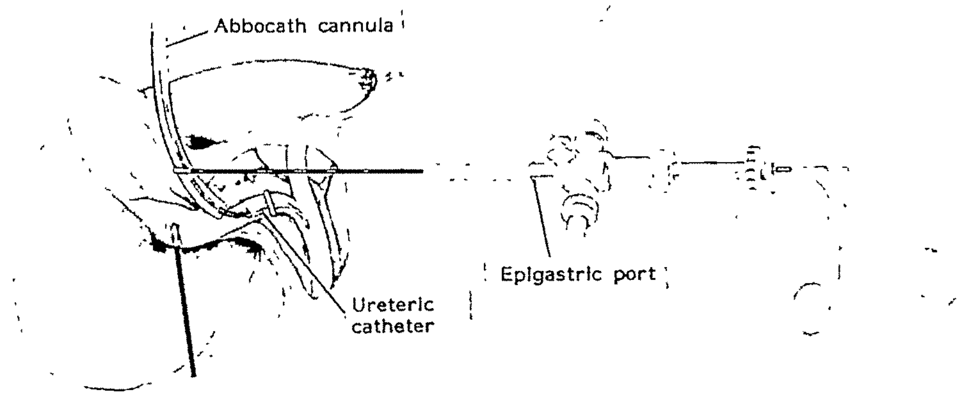

Figure 1 *The Abbocath cannula is guided to an incision in the cystic duct, and a 4-Fr ureteric catheter is inserted into the duct through the cannula. The ureteric catheter is held in position with a clip*

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Short note

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Endoscopic sphincterotomy, nasobiliary drainage and biliary stent placement without image intensification

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Endoscopic sphincterotomy (ES) is a useful therapeutic procedure in the management of choledocholithiasis[1,2], gallstone pancreatitis[3,4], acute cholangitis[5] and biliary dyskinesia[6–9]. Nasobiliary drainage and biliary stent placement complement this procedure[10–17]. These treatments are usually carried out using an image intensifier, but such equipment is expensive and may not be available in developing countries. Methods and results of ES, nasobiliary drainage and biliary stent placement performed without the aid of an image intensifier are reported.

Patients and methods

Between January 1990 and August 1991, 175 consecutive patients suspected of having pancreatobiliary disorders underwent endoscopic retrograde cholangiopancreatography (ERCP). Nineteen patients underwent ES, five nasobiliary drainage and six had biliary stents placed All procedures were performed by one endoscopist without the aid of an image intensifier.

ES was performed using an Olympus KD-22Q (Olympus, Tokyo, Japan) papillotome and electrosurgical unit (Olympus PSD-2/UES-10). The position of the papillotome was confirmed by injecting a small amount of contrast material and exposing a film. When the common bile duct (CBD) was clearly visualized, the papillotome was withdrawn, leaving 50 per cent of the papillotome wire visible outside the papilla. It was then bowed and the papilla cut using blended diathermy current. Patients were observed for at least 24 h and if no complications were noted were discharged. ERCP was performed 2–3 weeks later to check for ductal clearance in patients with choledocholithiasis

Results

ERCP was successful in 168 patients (96 per cent). Two attempts were required in four patients; six of the seven failures were encountered in the first ten patients.

ES was performed successfully in 17 patients but the papillotome could not be positioned in the CBD in two. The 13 patients with choledocholithiasis in whom ES was performed had the CBD cleared of stones. One patient in whom ES was performed for suspected gallstone-induced acute pancreatitis improved dramatically after sphincterotomy and recovered completely.

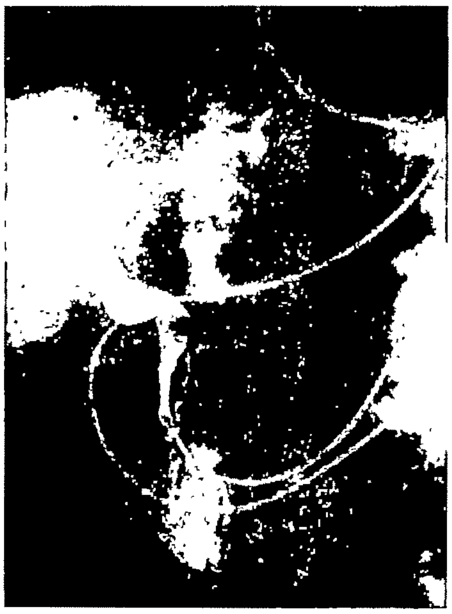

Figure 1 *Nasobiliary drainage in a patient with choledocholithiasis and acute cholangitis*

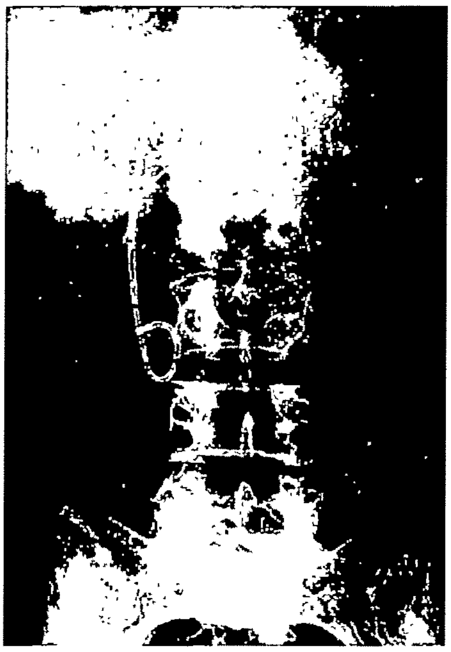

Figure 2 *Biliary stent in a patient with carcinoma of the head of the pancreas*

ES was also successful in a patient with periampullary carcinoma in facilitating biopsy of the tumour and in two other patients for placement of biliary stents.

No procedure-related complications were seen. Nasobiliary drainage was successfully carried out in five patients using a

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catheter (ENBD-6; Wilson–Cook Medical, Winston-Salem, North Carolina, USA) without sphincterotomy. All patients had acute cholangitis, in three from choledocholithiasis (*Figure 1*) and in two caused by malignant obstruction

Biliary stent placement was attempted in six patients with malignant CBD obstruction using double-pigtail stents (ZEBD-6/7; Wilson–Cook Medical). Two patients had hilar obstruction caused by carcinoma of the gallbladder and four had cancer of the head of the pancreas. Stents were successfully placed across the obstruction (*Figure 2*). Two patients required ES, one required a precut needle knife papillotomy and all were relieved of pruritus.

Discussion

This study shows that, although not ideal, ERCP, ES, nasobiliary drainage and biliary stent placement can all be successfully performed without the aid of an image intensifier.

Although the numbers are small, the high success rate for ES, ductal clearance, nasobiliary drainage and stenting are comparable to those noted by others[1,2].

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Aggressive angiomyxoma of the perineum and pelvis

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Aggressive angiomyxoma is a rare distinctive soft tissue tumour that is predominantly found in the perineum and pelvis of young women. This paper presents two cases and a review of the literature.

Case reports

Patient 1

A 47-year-old woman presented with a short history of non-tender swelling in the left buttock (*Figure 1*). There was a cough impulse and the diagnosis of a perineal hernia was considered. Computed tomography (CT) showed a pelvic mass (20 × 10 cm) confluent with the rectal wall, vagina and urethra. Excision was performed by a combined pelvic and perineal approach, and histological examination showed aggressive angiomyxoma. Serial CT scans showed no evidence of residual disease until 2 years later, when a scan showed a 3 × 5 cm mass related to the ischiorectal fossa. At a further 2 year follow-up, this was unchanged in size

Patient 2

A 77-year-old woman presented with a smooth swelling (10 × 8 cm) of the left thigh and a swollen leg Results of cytology of the aspirated opaque gelatinous fluid were normal. Venography (undertaken to exclude an iliofemoral thrombosis) was normal, but CT demonstrated a large pelvic mass (*Figure 2*) extending down the posterior compartment of the thigh. Open biopsy revealed grey gelatinous material, the histology of which indicated aggressive angiomyxoma. The widespread extent of the disease precluded further surgery.

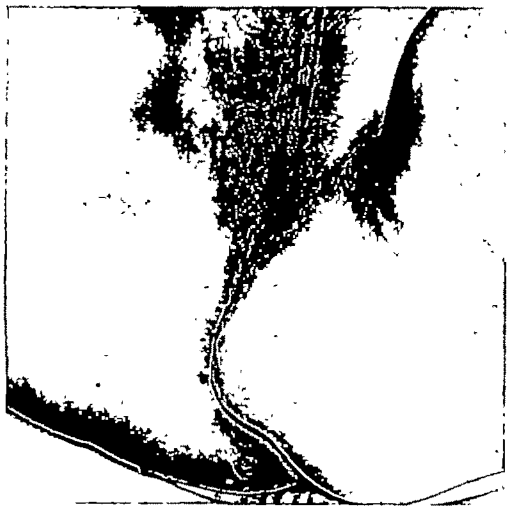

Figure 1 *Left ischiorectal swelling in patient 1*

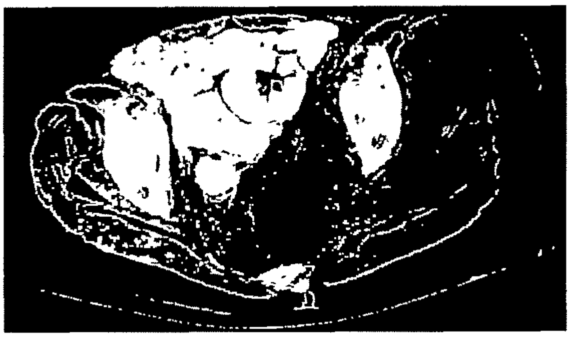

Figure 2 *Computed tomography in patient 2 showing the extent of the extrapelvic component*

Discussion

Aggressive angiomyxoma of the perineum and pelvis has only recently been recognized as a separate histopathological entity. Steeper and Rosai[1] were first to describe this distinctive pelvic tumour. First thought to occur exclusively in young women, aggressive angiomyxoma has since been reported in older women and men[2]. These uncommon tumours are characterized by a bland myxoid and vascular stroma that is locally aggressive. Although few cases of aggressive angiomyxoma have been described[3], Steeper and Rosai[1] noted that such tumours had been reported as early as 1863 as lipomas, myxomas, fibromas and vascular myxomas. The cell of origin has been suggested to be the myofibroblast[1] or fibroblast[2] of the pelvic connective tissues.

Aggressive angiomyxomas are usually polypoid and most often confined to the vulva, pelvic floor and perineum[1-3], but they may present with symptoms and signs suggestive of an obturator[1] or perineal[4,5] hernia, as in the first patient presented. Patient 2 represents the oldest and most extensive case of aggressive angiomyxoma reported. The term 'aggressive' was added as a prefix to the histological classification of angiomyxoma[1] to emphasize the potential of these tumours to recur locally. Indeed, local recurrence is as much a hallmark of aggressive angiomyxoma as is its bland histological appearance[1,2]. This fact is not surprising as the tumour blends imperceptibly with the surrounding tissue and does not elicit formation of a capsule, making adequate surgical clearance awkward. Despite the propensity of aggressive angiomyxoma to be locally persistent, there is no evidence that it metastasizes as do the sarcomas it resembles[1-3]. Well planned wide excisional surgery is the treatment of choice for primary or recurrent disease.

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Significance of intracystic pressure in abdominal hydatid disease

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A prospective study was performed in 32 patients (24 female, eight male) with 50 abdominal hydatid cysts, to assess whether intracystic pressure (ICP) could predict viability. The median ICP, measured during operation, was 35 cmH_2O *for 31 viable cysts and zero for nine non-viable cysts located in the liver* ($P<0\cdot05$)*. The median ICP was significantly higher in cysts located in the left lobe of the liver than in those in the right* ($P<0\cdot05$)*. The ICP was not significantly different in unilocular or multilocular cysts. ICP increased as the diameter of the cysts increased. The sensitivity of the indirect haemagglutination test was 86 per cent and the specificity 75 per cent. It is concluded that measurement of ICP is a simple and reliable method for assessment of the viability of abdominal hydatid cysts.*

Hydatid cyst is a parasitic infection caused by *Echinococcus granulosus*. This disease is endemic in Turkey[1–4]. Surgical treatment is still the preferred approach, although progress is being made in the medical treatment of hydatid disease[5–7].

While surgery is indicated for viable cysts, no treatment is usually required for degenerated or calcified cysts[8,9]. Preoperative assessment of cyst viability is by biochemical and radiographic studies, but false-positive and false-negative results may occur. Furthermore, the surgeon may have difficulty at operation in determining the viability of the cyst.

Hydatid cysts have been known since the time of Hypocrates, who defined the disease as a 'liver full of water'. This 'water' has not received adequate attention and studies of cystic fluid and intracystic pressure (ICP) are rare and inconclusive[8,10].

In this prospective study of 50 abdominal hydatid cysts, the relationship between ICP and viability was investigated

Patients and methods

The study included 32 patients (24 female, eight male) with 50 intra-abdominal cysts. Their mean age was 38·8 (range 7–78) years. Of the cysts, 40 (80 per cent) were located in the liver, two (4 per cent) in the spleen and eight (16 per cent) in different parts of the abdomen Before operation the indirect haemagglutination test, ultrasonography or computed tomography was performed.

At operation, after exposure of the cyst and before any manipulation, ICP was measured from the apex of the cyst A 16-G needle was connected to a water manometer and after puncture of the cyst the pressure was recorded in centimetres of water The needle was not perfused. While carrying out this procedure the abdominal cavity was protected with pads soaked in hypertonic saline After recording the pressure, the same needle was used to aspirate the cyst and for instillation of hypertonic saline to inactivate it Together with the pressure within the cyst, the diameter, location, unilocular or multilocular nature of the cyst, and the characteristics of the fluid within it were noted

Cysts were deemed viable if the intracystic fluid was clear and daughter cysts with scolices were present The cyst was considered non-viable if the intracystic fluid was turbid, the germinative membrane was degenerate, or the cyst was calcified or grossly infected.

For the treatment of cysts, different surgical techniques such as cystectomy, partial cystectomy and capitonnage (suture obliteration), omentoplasty, external tube drainage, or primary closure were employed as indicated.

The Mann–Whitney *U* test was used for statistical analysis Correlation between cyst diameter and ICP was analysed using Durbin–Watson regression analysis.

Results

Of the 40 cysts located in the liver, 31 were viable and nine non-viable. The median ICP was 35 (range 8–75) cmH_2O in viable cysts and 0 (range 0–2) cmH_2O in non-viable cysts ($P<0\cdot05$). The median pressure in cysts located in the right lobe was 32 cmH_2O, while that for those in the left lobe was 50 cmH_2O ($P<0\cdot05$). The ICPs were 8 and 28 cmH_2O in two splenic cysts. The median pressure was 24 cmH_2O for seven viable cysts located in different parts of the abdominal cavity (*Table 1*).

The median ICP was 34 (range 12–62) cmH_2O in 14 viable unilocular cysts and 35 (range 8–75) cmH_2O in 17 viable multilocular hepatic cysts ($P>0\cdot05$).

There was a direct correlation between viable cyst diameter and ICP, which increased with cyst size (regression equation $y=26\cdot8+0\cdot96x$; $r=0\cdot32$, $P<0\cdot05$) (*Figure 1*). The mean diameter of cysts located in the right lobe was 8·8 (range 5–20) cm, while that of those in the left was 12·1 (range 5–25) cm.

Before operation the indirect haemagglutination test result was positive in 19 of 25 patients in whom it was performed. Viable cysts with high ICP were found in 18 of 19 patients with a positive test. In one patient the cyst was degenerate and the ICP was zero. In three of the six patients with a negative indirect haemagglutination test result the cysts were calcified or infected and non-viable, with zero ICP; the other three patients with a negative result had five cysts which were all viable. The

Table 1 *Intracystic pressure of abdominal hydatid cysts in relation to their location and viability*

	Viable cysts		Non-viable cysts	
Location	No.	Median ICP (cmH_2O)	No.	Median ICP (cmH_2O)
Liver	31	35 (8–75)	9	0 (0–2)
Right lobe	24	32 (8–58)	7	0 (0–2)
Left lobe	7	50 (15–75)	2	— (0–1)
Spleen	2	— (8–28)	0	— —
Other	7	24 (12–67)	1	— (0)
Total	40		10	

Values in parentheses are ranges. ICP, intracystic pressure

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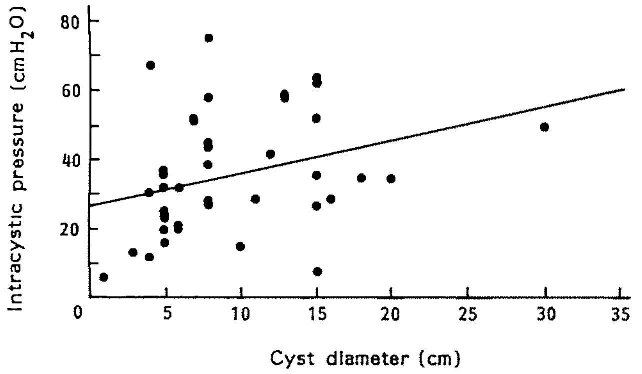

Figure 1 *Relationship between intracystic pressure and diameter of viable cysts located in liver* (n=*31*), *spleen* (n=*2*) *and elsewhere* (n=*7*) *Regression equation* $y=26{\cdot}8+0{\cdot}96x$, $r=0{\cdot}32$, $P=0{\cdot}045$ (*Durbin–Watson test*)

sensitivity of the indirect haemagglutination test was thus 86 per cent and the specificity 75 per cent.

Discussion

Assessment of the viability of hydatid cysts is important when deciding on correct management, and difficulty in making this assessment may arise before or during operation. Preoperative serological tests are positive in approximately 85–89 per cent of cases[1,3,8]. Intracystic fluid and pressure have been little studied. The ICP ranges from 30 to 80 cmH$_2$O[8,10]. This raised pressure has been blamed for the high complication rate, and contrasts with the low ICP of non-parasitic hepatic cysts.

At operation, gross infection or a degenerated germinative membrane may indicate non-viability. While calcification is a sign of non-viability, the cyst may be viable with minimal peripheral calcification[9].

Viability can be more reliably assessed microscopically by the eosin exclusion test or flame cell activity of the protoscolices. However, this is not possible for all viable cysts[11,12]. These tests were carried out in only a small minority of patients towards the end of the present study, and proved difficult in practice.

The gross characteristics of the cyst are reliable for the assessment of viability, and in recent years ultrasonography has been used to assess viability[13].

The median ICP in the present cases was 35 cmH$_2$O for viable and zero for non-viable hepatic cysts. The unilocular or multilocular nature of the cyst did not affect the pressure, but ICP did rise as the diameter of the cyst increased.

Cysts located in the left lobe of the liver had a higher ICP than those in the right. This reflects differences in the diameters of the cysts, which were larger in the left lobe.

In the present patients the indirect haemagglutination test had a positivity of 86 per cent and a specificity of 75 per cent. Therefore the surgeon must expect some false-positive and false-negative predictions of viability based on this test.

In conclusion, measurement of ICP during operation is a simple and reliable method for assessing the viability of hydatid cysts. Because of the risks of dissemination of the disease and anaphylaxis from leakage, percutaneous measurement of ICP must be discouraged. Low ICP indicates non-viability of the cyst while a high pressure indicates viability. ICP was found to be a more reliable measure than the indirect haemagglutination test in the assessment of cyst viability.

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Open method *versus* capsulorrhaphy without drainage in the treatment of children with hepatic hydatid disease

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A recognized major postoperative complication of hepatic hydatid disease is accumulated hydrops leading to secondary infection in the residual cavity of the excised cyst. This study examined two methods of treating cystic hepatic hydatid disease in 43 children. A group of 22 children were treated by a new method of open drainage; 21 underwent capsulorrhaphy without drainage. There was no mortality or morbidity. The open method was associated with more rapid resolution of hydrops and quicker shrinkage of residual cavities, with efficacy over a median follow-up of 42 months.

Cystic hydatid disease caused by *Echinococcus granulosus* is a parasitic zoonosis found in 22 provinces of the Chinese mainland. It is endemic in North-western China including Sinkiang, Chinghai, Kansu, Tibet and Inner Mongolia[1]. Humans as intermediate hosts of the larval stage become infected with the disease by ingestion of the ova, which develop into cysts in any of the viscera, most commonly the liver (50–70 per cent of cases)[2]. Hepatic infestation occurs at any age, but most patients are probably infected in childhood[3]; children account for over 20 per cent[1] of patients with hydatid disease in China.

The first cases of hydatid cyst in this country were reported[4] at Tsingtao, Shantung province, in 1905. Reported levels reached serious proportions from 1950 to 1970. By 1984, 15 888 patients had been treated surgically in China as a whole, of which 9607 (60·5 per cent) were in Sinkiang[5]. Hydatid disease is endemic throughout the whole region of Sinkiang, where the lowest seropositive rate of the investigation was 3·1 per cent[6] The expected number of surgical cases[5] was at least 1000 per year and the disease was one of the most important parasitic infestations in the region.

Between 1953 and 1985, 775 patients with 1156 hepatic hydatid cysts were treated by puncture aspiration of cyst contents, injection of antiscolicidal agents, reaspiration, removal of the endocyst, and a variety of methods for handling residual cavities including capsulorrhaphy without drainage (partial pericystectomy) in 914 (79·1 per cent), cyst omentoplasty or myoplasty in 107 (9·3 per cent), external drainage in 46 (4·0 per cent) and subtotal pericystectomy in 31 (2·7 per cent)[7]. The results were not satisfactory and after operation secondary infection of the residual cavities forming hepatic abscess occurred in 48 patients (6 2 per cent) after capsulorrhaphy without drainage This study investigates the treatment of 22 children by direct open drainage of the cavities into the peritoneal cavity to avoid secondary infection.

Patients and methods

Patients

Between January 1986 and December 1989, 43 children with hepatic hydatid disease, aged 2–14 years, were treated. The patients were divided into two groups: group 1 (eight boys, 14 girls) had the residual cavity treated by open drainage; group 2 (seven boys, 14 girls) underwent capsulorrhaphy without drainage There was no significant difference in age between the groups.

Preoperative preparation

Diagnosis was achieved by:

1. A history of living in a prevalent area of hydatid disease (all 43 children) and of contact with dogs (39)
2. Clinical manifestation (*Table 1*).
3. Immunodiagnostic methods – intradermal sensitivity test, indirect haemagglutination, enzyme-linked immunosorbent assay and latex-leptospiral agglutination *Table 2* shows the results.
4. Ultrasonography – hepatic and abdominal B-mode ultrasonography was performed in both groups. A total of 35 cysts were visualized in group 1 and 46 in group 2 There was no significant difference in size and ultrasonographic appearance between the two groups.
5. Computed tomography (CT) – CT scans were obtained in seven patients (group 1, four; group 2, three).

The number and localization of the cysts was made by ultrasonography to determine the incision before surgery The volume of the cysts was estimated from measurement of the oval or spherical cyst diameter

Surgical technique

Surgery was performed according to tumour-free operative principles[8]. The operative field was carefully protected from hydatid fluid spillage using packs and waterproof towels. Hydatid fluid and 'sand' was evacuated by needle aspiration and electric suction devices The injection volume of 10 per cent formalin solution as a scolicidal agent was not in excess of the aspirated volume of hydatid fluid After 5 min the solution was aspirated and the exocyst opened The endocyst was removed and any residual fluid aspirated. The residual cavity was rubbed with a gauze sponge soaked in 1 per cent formalin solution so that any scolices adherent to the exocyst wall were killed. The exocyst wall protruding from the liver was excised. In group 1 the residual cavity was left directly open into the peritoneal cavity. Group 2 patients underwent capsulorrhaphy without drainage.

The right lobe of the liver was found to be involved more often than the left (group 1, 15 patients, group 2, 12). Both lobes were involved in seven children (group 1, four, group 2, three) A single cyst was found in 31 patients (group 1, 14; group 2, 17) and multiple cysts in 12 (group 1, seven, group 2, five). The cyst contents were clear fluid and the endocysts were uncomplicated and new The removed cysts varied from 3 to 20 cm in diameter

Postoperative management

All children were treated with oral mebendazole in doses of 50–100 mg kg^{-1} day^{-1} for 28–30 days after surgery Patients were given three courses of medication separated by monthly rests.

Every child in group 1 was followed by ultrasonography twice in the first year and once a year thereafter

Results

No anaphylactic reaction or formalin toxicity was observed. There was no operative death. Patients in group 1 made a rapid recovery with shrinkage of the residual cavities. There were no complications after surgery and the mean hospital stay was 8·5 days. *Table 3* shows the patient details of the two groups at discharge. All children in group 1 were followed for 24–60 (median 42) months without recurrence

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Table 1 *Clinical manifestations of hepatic hydatid disease in 43 children*

	No
Symptoms	
Epigastric pain	23
Anorexia	11
Fever	6
Chill with fever	2
Jaundice	2
Asymptomatic carriers	20
Signs	
Hepatomegaly	31
Epigastric mass	25
Epigastric pressure pain	10
Malnutrition	7
Hydatid thrill	4

Table 2 *Results of immunodiagnostic methods*

Method	No. of patients positive ($n=43$)
Intradermal sensitivity test	35
Indirect haemagglutination	29
Enzyme-linked immunosorbent assay	27
Latex-leptospiral agglutination	26

Table 3 *Comparison of the two methods of treatment*

	Group 1 (open method; $n=22$)	Group 2 (capsulorrhaphy, $n=21$)
Postoperative recovery*		
Time to restoration of normal temperature (days)	5·9	11·2
Hospitalization (days)	8·5	14·7
Ultrasonographic follow-up		
Without residual cavities	6	0
Residual cavities		
With ½ reduction in size	12	15
With ⅓ reduction in size	17	24
Without reduction in size	0	7
Total	35	46

*Values are means

Discussion

Hydatid disease in children is unusual in developed countries in which sheep are farmed[9], but frequent in Sinkiang. The most commonly affected organs are the liver and lung. Most children tend to be infected by contact with dogs, although some are indirectly infected by eating food contaminated with the parasitic egg. Cysts in the liver may remain asymptomatic for a number of years and presenting symptoms and signs, such as epigastric discomfort, jaundice, and biliary colic, are related to the mechanical effects of growth and compression of adjacent parenchyma and ducts[10]. Fever may be caused by infection of the cysts.

The disease incidence in children has increased over the past few years[11]. Todoroff *et al.*[12] indicated that the seropositive rate in children was lower than in adults. Newer and more specific serological tests have enhanced diagnosis in children. CT is more accurate than ultrasonography in preoperative management[13].

Systemic toxicity has been recorded following the use of formalin[14], local toxicity after using cetrimide[15], and sclerosing cholangitis can occur following the use of formalin, hypertonic saline, and silver nitrate[16–18]. If formalin is injected before aspirating the hydatid fluid, it may result in toxicity and sclerosing cholangitis. If the cyst is without a fistula and infection, formalin can be used as a scolicidal agent. If a fistula or infection has occurred, another scolicidal agent, such as hypertonic saline, is injected.

Surgery is still an effective method of management. Hepatic resection may be indicated where the liver parenchyma of one lobe is destroyed, a bilobar cyst is present, a bilobar cyst is found close to the vascular pedicle, or if there are multiple cysts[19,20]. Total pericystectomy may lead to a high incidence of postoperative bleeding, bile leakage and other complications[21].

A residual cavity is left after extirpation of an endocyst. The classic treatment of the cavity was capsulorrhaphy without drainage. Modifications such as partial pericystectomy, omentoplasty or myoplasty, and a variety of techniques of external drainage have been used. Hydrops, consisting of the exudation of blood and bile from partial intrahepatic ducts in the exocyst wall, may be accumulated in the cavity. The exocyst wall is usually composed of hard fibrous connective tissue but the inner cavity surface may be covered with soft areolar tissue after surgery[22]. This tends to prolong time to collapse of the cavity and leads to secondary infection. Barros[23] reported a 1·4 per cent incidence of such infection in a series of 212 patients. Saidi and Nazarian[24] described a method of freezing a funnel to the exocyst wall and opening the latter with a residual cavity directly open to the peritoneal cavity.

The open method described in this paper was previously avoided because of the possibility of complications (persisting fistula and infection)[25,26]. In adults the complications are more frequent in those undergoing open drainage because the endocyst communicates with the small biliary ducts in 80 per cent[26]. In children the cyst is in the early stage of the larval form and the pressure of the cyst fluid normally prevents detachment of the endocyst from the exocyst. If punctured during surgery, clear fluid is aspirated and this is known as an 'uncomplicated' cyst. In 22 of the 43 children, who underwent open drainage, 35 cysts were removed. All residual cavities were opened and no complications occurred during a 24–60-month follow-up. The residual cavity open method should be carried out if a partial extrahepatic uncomplicated hydatid cyst is found.

Recurrence occurs in 5–11 per cent of patients[13]. The principal measures taken to prevent recurrence include avoiding spillage of cyst contents, emptying the exocyst thoroughly at operation and using chemotherapy before and after operation.

Mebendazole, albendazole and other benzimidazole compounds offer a prospect of reducing or preventing recurrence[27,28]. Mebendazole is more effective in the early stage of the infection, in small cysts and in children[29,30]. At least 12 months is required after treatment to obtain an objective evaluation of the efficacy of benzimidazoles[31].

This study shows that treating the residual cavity by open drainage is an easy, safe and effective technique in the management of selected children with hepatic hydatid disease.

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In vivo assessment by videomicroscopy of acute renal microvascular responses to cyclosporin

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Nephrotoxicity limits the use of cyclosporin A for immunosuppression after organ transplantation and may be caused by glomerular hypoperfusion. Indirect studies have shown that cyclosporin A increases renal vascular resistance and reduces total renal blood flow. This study used direct in vivo *videomicroscopy to define the effects of the drug on the renal microcirculation of the rat. An intravenous infusion of cyclosporin A (20 mg per kg body-weight) caused a 13 per cent acute constriction of the proximal interlobular artery and an associated 29 per cent reduction in preglomerular interlobular arterial blood flow. There was a simultaneous increase in mean arterial blood pressure of 34 per cent caused by cyclosporin A and a 23 per cent increase in systemic vascular resistance. Cyclosporin acutely reduces renal microvascular blood flow by vasoconstriction and affects the central circulation, suggesting that a generalized peripheral vasoconstriction is induced.*

Cyclosporin A is the immunosuppressant of choice after organ transplantation. Used with steroids or alone, it improves allograft survival rates when compared with patients immunosuppressed with azathioprine and steroids[1,2]. The major limiting factor in the use of cyclosporin A is drug-induced nephrotoxicity[3], which may require conversion to immunosuppression with less effective drugs. Cyclosporin nephrotoxicity has a reported incidence of 30–74 per cent in cadaveric renal recipients[4,5] and is a chronic problem in 15 per cent of these patients[3].

The mechanism of cyclosporin A nephrotoxicity is incompletely understood. Administration of the drug decreases total renal blood flow and increases renal vascular resistance in experimental animals[6] and in humans[7]. The subsequent glomerular hypoperfusion may account for the observed decrease in the glomerular filtration rate, which leads to an increase in blood urea nitrogen and serum creatinine levels. This functional renal impairment has been observed acutely and chronically in animals[8,9] and humans[1,2,10]. Cyclosporin nephrotoxicity also occurs in the normal kidneys of extrarenal allograft recipients[11,12] and during use of the drug in the treatment of autoimmune disease[13]. This study was performed to define the acute responses of the renal microcirculation to cyclosporin A.

The split-hydronephrotic rat kidney model as described by Steinhausen *et al.*[14] was used to view the preglomerular renal microcirculation directly. This model allows *in vivo* visualization of the renal microcirculation and is effective in the assessment of renal microvascular responses to known vasoactive substances.

Materials and methods

Male Sprague–Dawley rats (Charles River Laboratories, Portage, Michigan, USA) were maintained at an animal care facility with free access to water and rodent chow (Purina Mills, Louisville, Kentucky, USA). All experiments were performed with the approval of the University of Louisville Animal Care and Use Committee.

Induction of hydronephrosis

Six weeks before acute microvascular experiments, the rats were anaesthetized with a single intramuscular injection of ketamine (7·5 mg) and xylazine (3 mg). A midline laparotomy was performed under sterile conditions and the upper left ureter ligated with a 4/0 silk ligature Between 2 and 7 days before experiments, the hydronephrotic kidneys were inspected to assess their suitability for *in vivo* microscopy. The animals were anaesthetized as described above, and a left flank incision made under sterile conditions. Suitable kidneys showed no evidence of local infection and had a renal cortex sufficiently thin to permit transillumination.

Animal preparation

The mean(s.e.m) animal weight at the start of the microvascular experiments was 424(19) g. After a recovery period of at least 48 h, animals were prepared for microvascular study as previously described[15]. Anaesthesia was induced using intraperitoneal urethane (800 mg per kg body-weight) and α-chloralose (60 mg per kg body-weight) The animal was placed on an autoregulating heating pad to maintain rectal temperature between 36 and 37°C. A stereotactic precollicular mid-brain decerebration was performed[16] to study renal microvascular responses without the depressant effects of drug anaesthesia. An injection of 3 ml isotonic saline was administered subcutaneously to maintain hydration throughout surgery. Animals were then allowed 5–6 h to recover from anaesthesia[17].

Following decerebration, tracheostomy was performed for airway control. To determine cardiac output by transpulmonary aortic thermodilution[18], a thermistor (Series 500 probe; Yellow Springs Instruments, Yellow Springs, Ohio, USA) was placed in the proximal aortic root via the right carotid artery, and the right jugular vein cannulated using PE50 tubing (Fischer Scientific, Cincinnati, Ohio, USA)

The left femoral artery was cannulated and direct mean arterial pressure monitored. A left femoral vein cannula provided venous access for continuous isotonic saline infusion (1 ml/h) and intravenous drug administration.

The kidney was mobilized on the renal pedicle via a left flank incision without disturbing the normal neurovascular supply to the organ. Electrocautery was used to divide the kidney along the greater curvature. One-half of the organ was then gently stretched to its original size with 4/0 silk sutures over an optical port in an environmentally controlled 50-ml tissue bath. This contained a modified Krebs' solution at 280–290 mOsm/l comprised of $NaHCO_3$ (26 mmol/l), NaCl (133 mmol/l), KCl (5 mmol/l), $CaCl_2$ (3 mmol/l), KH_2PO_4 (1 mmol/l), $MgSO_4$ (1 mmol/l) and dextrose (12 mmol/l). The bath was maintained at 37°C and the pH at 7·4.

The preparation was positioned on the stage of a compound trinocular microscope (Nikon, Garden City, New York, USA) for

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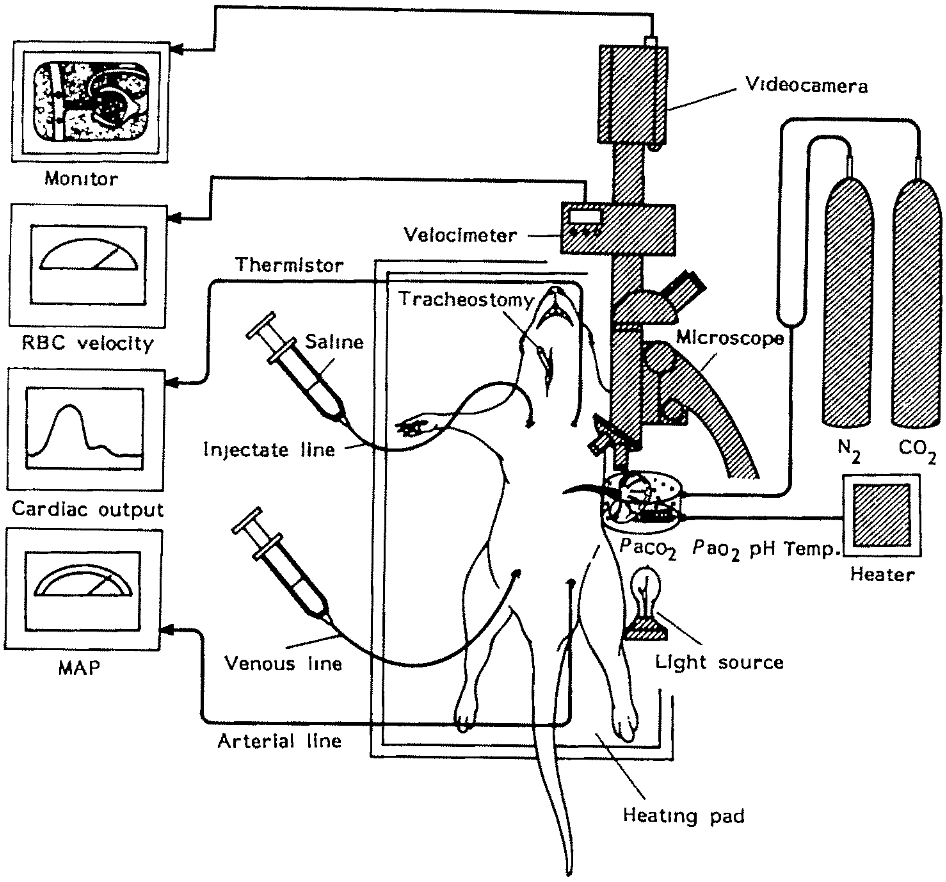

Figure 1 *Diagrammatic representation of the experimental model RBC, red blood cell MAP, mean arterial pressure,* P_{aO_2}, *arterial partial pressure of oxygen,* P_{aCO_2}, *arterial partial pressure of carbon dioxide*

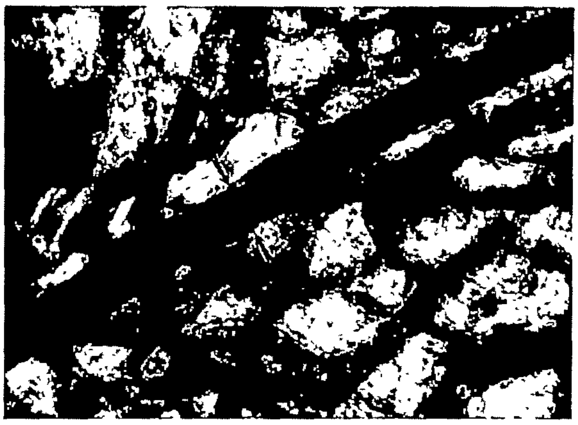

Figure 2 *Photomicrograph of the interlobular artery (arrows) as seen on closed-circuit television microscopy (Original magnification × 1500)*

direct and closed-circuit television microscopy (*Figure 1*). Microvascular images were transmitted via a colour camera (Model NC-8, NEC, Wood Dale, Illinois, USA) to a television monitor (Model CVM-1271; Sony, Park Ridge, New Jersey, USA) and a videocassette recorder (Model AG-7300; Panasonic, Arlington Heights, Illinois, USA).

The criteria for acceptance of the preparation were: (1) a stable mean arterial pressure of 75–115 mmHg; (2) a core temperature of 36–37·5°C; (3) a clear visualization of the renal microvessels for measurement; and (4) a brisk blood flow through all vascular segments.

Measurement of vessels

A proximal interlobular arteriole was identified on the videoscreen (*Figure 2*). This vessel was used as an indicator of microvascular blood flow because it lay immediately upstream of the afferent arteriole and was therefore a good indicator of glomerular perfusion.

Central intravital red blood cell velocity in the interlobular arteriole was measured using an optical Doppler velocimeter (Microcirculation Research Institute, Texas A & M University, College Station, Texas, USA). Videotape recordings of microvascular images were made, and the inner diameter of the interlobular arteriole measured afterwards directly from the television monitor screen using electronic calipers Microvascular blood flow in nanolitres per second was calculated using the formula:

$$\text{Blood flow} = (V/1{\cdot}6) \times (\pi r^2) \times (0{\cdot}001)$$

where V is the red blood cell velocity in millimetres per second, 1·6 is a factor to convert centre-line velocity into mean cross-sectional velocity[19], r is the vessel radius in micrometres, and 0·001 is a factor for conversion to nanolitres per second

Experimental protocol

After a 5-h period to allow for recovery from drug anaesthesia and at least 1 h to permit equilibration of the kidney preparation with the tissue bath[15], baseline measurements were made of microvascular diameter and red blood cell velocity, mean arterial pressure, cardiac output and heart rate. Systemic vascular resistance was calculated as MAP/CO, where MAP is the mean arterial pressure and CO the cardiac output. Variables were assessed at intervals for up to 1 h from drug administration

Animals were allocated to one of the following three groups:

1. Cyclosporin A ($n = 7$) – A total of 20 mg cyclosporin powder was dissolved in 0·14 ml ethanol and mixed with 1·86 ml 10 per cent Intralipid (Kabi Pharmacia, Alameda, California, USA) for 1 h at 35°C. Approximately 1 ml (20 mg per kg body-weight cyclosporin A equivalent) was then infused intravenously via the left femoral cannula at room temperature over 5 min
2. Vehicle ($n = 7$) – A volume of 1 ml vehicle solution (0·07 ml ethanol, 0·93 ml 10 per cent Intralipid) was infused intravenously over 5 min.
3. Saline ($n = 6$) – A volume of 1 ml isotonic saline was infused intravenously over 5 min

Statistics

Results are expressed as percentages of baseline values to allow for variability between baseline parameters. Measurements of microvascular diameters and cardiac output were made in triplicate over a 30-s period and the mean of the values taken Group data were pooled and the mean(s.e.m.) calculated. The means were evaluated as changes from baseline values and subjected to repeated measures analysis of variance and follow-up Dunnett's test. Between-group comparisons were made using one-way analysis of variance and Tukey's honestly significant difference. A value of $P < 0{\cdot}05$ was considered significant.

Although the sample sizes were small they were sufficiently large to satisfy normality assumptions based on the statistical models used

Results

Table 1 shows the baseline values for the variables measured; there were no statistical differences between the three groups. Intravenous infusion of 1 ml isotonic saline had no significant effect on central haemodynamics or the renal microcirculation. Results from this group demonstrated that mean arterial pressure, cardiac output and renal microvascular parameters remained stable under control conditions and each experimental animal acted as its own control. This allowed analysis of changes from baseline values within each group.

A 5-min intravenous infusion of 20 mg/kg cyclosporin A resulted in a rapid and persistent constriction of the proximal interlobular arteriole (*Figure 3*). Mean(s.e.m.) maximal constriction was 13(3) per cent ($P < 0{\cdot}01$ *versus* baseline) at 5 min (*Figure 3*). The arterial diameter gradually returned towards baseline throughout the experiments, but the vessel remained significantly constricted at 30 min ($P < 0{\cdot}01$ *versus* baseline). The emulsion vehicle by itself had no appreciable effect on arteriolar diameter, and interlobular arteriole diameters in the cyclosporin group were significantly less than those in both control groups for all times ($P < 0{\cdot}01$).

Table 1 *Baseline parameters*

	Controls		
	Saline ($n = 6$)	Vehicle ($n = 7$)	Cyclosporin A ($n = 7$)
Weight (g)	442(24)	412(20)	425(28)
Mean arterial pressure (mmHg)	98(6)	97(5)	93(6)
Cardiac output (ml/min)	105(3)	109(5)	127(8)
Heart rate (beats/min)	404(7)	413(19)	416(17)
Systemic vascular resistance (units)	0·94(0·07)	0·92(0·08)	0·75(0·07)
Interlobular diameter (µm)	38·6(3·1)	40·8(4·5)	36·3(2·9)
Interlobular flow (nl/s)	17·4(1·9)	21·9(7·6)	18·3(4·4)

Values are mean(s.e.m.)

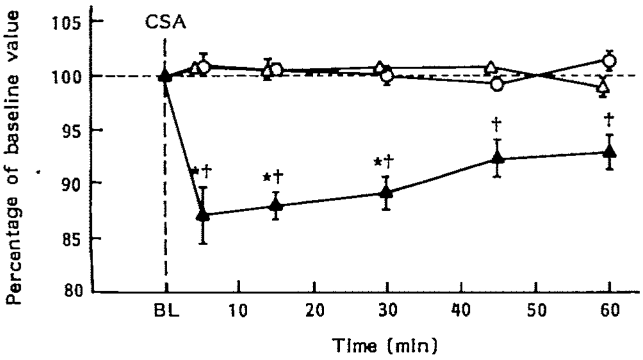

Figure 3 *Interlobular arteriolar diameter responses to intravenous saline* (○), *the Intralipid–ethanol vehicle* (△) *and 20 mg/kg cyclosporin A* (*CSA*) (▲). *Values are mean(s.e.m.) percentage of baseline* (*BL*). *P < *0·01* versus *baseline*, †P < *0·01* versus *both control groups*

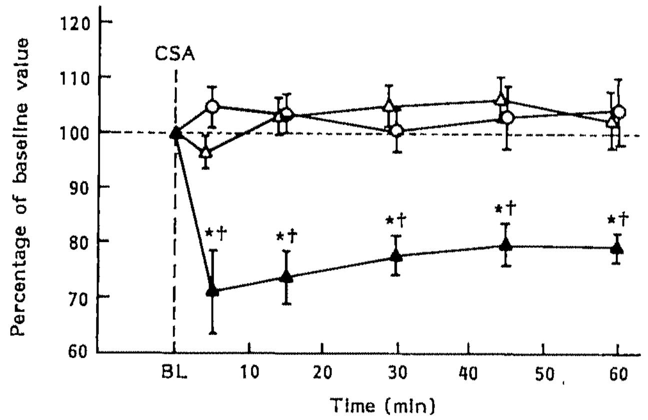

Figure 4 *Interlobular arterial blood flow responses to intravenous saline* (○), *the Intralipid–ethanol vehicle* (△) *and 20 mg/kg cyclosporin A* (*CSA*) (▲). *Values are mean(s.e.m.) percentage of baseline* (*BL*) *P < *0·01* versus *baseline*; †P < *0·01* versus *both control groups*

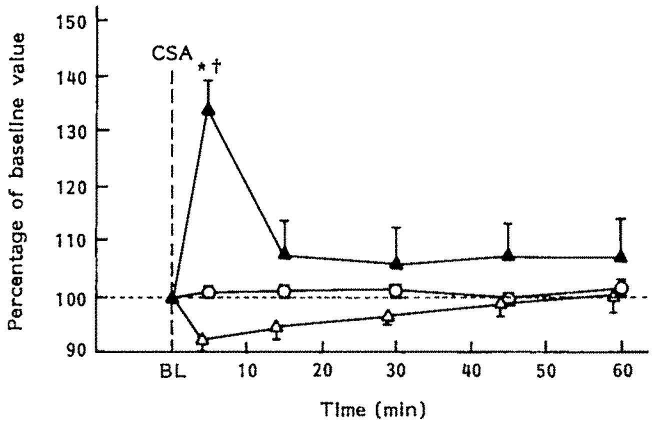

Figure 5 *Mean arterial pressure changes following administration of intravenous saline* (○), *the Intralipid–ethanol vehicle* (△) *and 20 mg/kg cyclosporin A* (*CSA*) (▲). *Values are mean(s.e.m.) percentage of baseline* (*BL*) *P < *0·01* versus *baseline*, †P < *0·01* versus *both control groups*

Preglomerular microvascular blood flow in the proximal interlobular arteriole was maximally reduced by 29 per cent at 5 min in the cyclosporin A group (*Figure 4*). Values at all times were significantly less than those in both control groups ($P < 0{\cdot}01$). The emulsion–ethanol vehicle tended to increase microvascular blood flow, and the true magnitude of impairment of blood flow caused by cyclosporin A may have been greater than the observed reduction.

Cyclosporin infusion resulted in an acute hypertensive response with an increase in mean arterial pressure by 34 per cent at 5 min (*Figure 5*). This was accompanied by a 23 per cent increase in calculated systemic vascular resistance and a transient increase in cardiac output. These haemodynamic alterations were not observed in rats receiving vehicle: these animals became slightly hypotensive. The maximum decrease in mean arterial pressure was 8 per cent, which was probably caused by peripheral vasodilatation by the ethanol component of the vehicle.

Discussion

The mechanism of cyclosporin-induced impairment of renal function remains incompletely understood. Histological and ultrastructural changes are minimal[9,20] and do not adequately explain the functional impairment of glomerular filtration. The concept that cyclosporin A impairs renal blood flow, reducing glomerular filtration rate and causing tubular hypoxia, was introduced by Baxter *et al.*[21]. It has been confirmed in animal studies using ultrasonographic flow probes at the renal artery[22], or radiolabelled isospheres to assess total renal blood flow[6]. Other studies have used clearance methods of estimating renal blood flow in humans[23] and animals[6,8] to show a reduction in total renal blood flow by cyclosporin A. Previous microvascular studies[24] have used immunofluorescence techniques to assess subcapsular renal blood flow responses to cyclosporin in mice semiquantitatively. Using an isolated perfused rat kidney model, Luke *et al.*[25] and Besarab *et al.*[26] showed that cyclosporin A raised renal vascular resistance, probably from an intrarenal vasoconstrictive effect. Both groups found that the cyclosporin vehicle Cremophor EL (Sigma Chemicals, St Louis, Missouri, USA) increased renal vascular resistance. This study, therefore, directly assessed the acute *in vivo* effect of parenteral cyclosporin A on the renal microcirculation and preglomerular microvascular blood flow.

One crucial issue in the interpretation of these results is the functional status of the hydronephrotic kidney preparation The microanatomy of the afferent arteriole is similar to that of the same vessel from a normal kidney[27], and the preglomerular and postglomerular vessels of this preparation have been shown to react appropriately to vasoactive substances when compared with indirect results obtained from normal kidneys[28,29]. This model is therefore an appropriate one to study the responses of the renal microcirculation to vasoactive substances.

Cyclosporin A acutely reduces preglomerular renal microvascular blood flow by 20–30 per cent, brought about by a 10–15 per cent vasoconstriction of preglomerular vessels. These alterations must be interpreted in the light of the observed changes in central haemodynamics. Since an acute hypertensive response to 20 mg/kg cyclosporin A was seen, accompanied by significant but less dramatic increases in cardiac output and calculated systemic vascular resistance, it is possible that some of the microvascular responses were attributable to renal vascular autoregulation as a result of increased perfusion pressure. Significant alterations in systemic haemodynamic parameters using cyclosporin A dissolved in Cremophor EL–ethanol solvent[15] have been reported; the vehicle itself caused considerable haemodynamic effects. In this study, a less toxic vehicle was used to dissolve the drug but alterations in haemodynamics were still observed. When cyclosporin A is infused intravenously over 5 min there is an acute increase in systemic blood pressure and peripheral vasoconstriction, similar to that seen in the renal microcirculation. This might be responsible for cyclosporin-related hypertension.

These results indicate that cyclosporin A acts as a vasoactive substance within the renal microcirculation. The pathophysiological mechanisms behind the observed vasoconstriction are unknown and require further investigation

The concept that cyclosporin A acts as a peripheral vasoconstrictor on vascular smooth muscle to increase systemic and renal vascular resistance is supported by evidence that the drug will contract aortic rings *in vitro*[30]. The intrarenal vasoconstriction and reduction in microvascular blood flow is of a magnitude that suggests a preferential effect on the renal microcirculation. This favours the hypothesis of an alteration in the balance of local humoral mediators in the kidney such as the vasoconstrictor prostaglandin thromboxane A_2, which has been shown to be increased during chronic cyclosporin administration in animals[31] and humans[23,32]. Thromboxane receptor antagonism only partially reverses cyclosporin A nephrotoxicity in rats[33]. The formation of prostaglandins is closely linked through common receptor mechanisms to the local production of angiotensin II. The possibility that cyclosporin A stimulates local angiotensin II formation, or directly stimulates the angiotensin II receptor, should be considered.

The chronic effect of cyclosporin A may be different. The drug may cause arteriolar damage[34] when administered chronically, although the functional impairment in patients is usually reversible and dose dependent[3].

Acknowledgements

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Liver transplantation for fulminant hepatic failure and late-onset hepatic failure in children

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The mortality rate of fulminant hepatic failure (FHF) and late-onset hepatic failure (LOHF) in childhood has remained between 70 and 95 per cent despite recent improvements in medical therapy. Liver transplantation has become an important therapeutic option in adults with this condition but has been performed infrequently in children. Between March 1988 and August 1991, 12 children aged between 1 month and 14 years with FHF or LOHF received 13 liver transplants. The aetiology was viral hepatitis in eight children (non-A non-B in six, A in two), drug hepatotoxicity (carbamazepine) in two, autoimmune hepatitis in one and congenital haemochromatosis in one. Reduced-size livers were used for ten of the 13 transplants. Morbidity after operation included infective complications and abdominal bleeding. Two patients died from graft versus *host disease, one from brain aspergillosis and another from graft infarction after portal vein thrombosis. Eight patients survive after a median follow-up of 18 months. Liver transplantation should be the therapeutic choice for children with FHF and LOHF for whom the chances of recovery are poor.*

Fulminant hepatic failure (FHF) is an infrequent and catastrophic illness in children. It is characterized by widespread necrosis of hepatocytes and caused by a wide variety of hepatic insults. The condition, as defined by Trey and Davidson, requires the development of hepatic encephalopathy within 8 weeks of the onset of illness in an individual with no evidence of previous liver disease^{1}. A similar clinical syndrome in patients whose encephalopathy does not occur until 8 weeks to 6 months after the onset of symptoms was reported from this centre as late-onset hepatic failure (LOHF)^{2}. The mortality rate for FHF and LOHF in children has remained between 70 and 95 per cent despite recent improvements in medical therapy$^{3-5}$.

Liver transplantation is increasingly accepted as a treatment for adults$^{6-9}$. Experience in children is scarce, mainly because of rapid evolution of illness and lack of paediatric donor livers. The present paper reports experience of liver transplantation for the management of FHF and LOHF in 12 children.

Patients and methods

From March 1988 to August 1991, 186 patients received 211 orthotopic liver transplants at King's College Hospital. Twelve children underwent transplantation for FHF or LOHF. There were six girls and six boys with a mean age of 5 years (range 1 month to 14 years). The cause of hepatic failure was acute viral hepatitis in eight children (six non-A non-B, two A), carbamazepine hepatotoxicity in two, autoimmune hepatitis in one and congenital haemochromatosis in one. Seven children had FHF and five LOHF (*Table 1*).

All children received full appropriate intensive care. Coagulation disorders were corrected with plasma, cryoprecipitate infusion or exchange transfusion. Endotracheal intubation was instituted when patients were in grade III or IV encephalopathy. Intracranial pressure was monitored in children with cerebral oedema. Mannitol and thiopentone infusions were used to reduce the intracranial pressure. The decision to transplant was taken according to previously published criteria^{10} provided no absolute contraindication to transplantation existed, such as active sepsis (pneumonia or positive culture not treated with appropriate antibiotics for 48 h), refractory systemic hypotension, or evidence of impaired brain stem function as a consequence of cerebral oedema. Six children had three criteria, and six had four or more criteria for transplantation. The children presented with hyperbilirubinaemia, with a mean total serum bilirubin concentration of 410 (range 87–632) mmol/l, and a mean aspartate aminotransferase level of 1392 (range 26–6000) units/l. Five were in stage II encephalopathy, five in stage III and two in stage IV. All had severe coagulopathy with prolongation of prothrombin time, with a mean value of 64 (range 27–130) s. With correction of the coagulopathy by plasmaphaeresis the prothrombin time was decreased to a mean of 15 s at the time of transplantation.

Orthotopic and reduced-size liver transplantations were performed according to accepted techniques^{11,12}. Venovenous bypass was not used. Baseline immunosuppression was achieved with cyclosporin A, steroids and azathioprine. The dosage of cyclosporin A was adjusted according to daily radioimmunoassay levels to maintain a trough concentration of 150–200 ng/ml. Episodes of allograft rejection were treated with pulse doses of steroids.

Results

Transplantation was performed 1–9 (mean 3) days after the patient was listed in the emergency category with the UK Transplant Service. Thirteen liver transplants were performed in 12 children, one requiring retransplantation after 6 months because of severe biliary obstruction. Three children underwent transplantation with full-size liver grafts, and nine with ten reduced-size livers, using the left lobe in six and the left lateral segment in four. Owing to rapid deterioration, two ABO-incompatible grafts were transplanted (*Table 2*).

The operation was technically uncomplicated because of the absence of portal hypertension and previous abdominal surgery. The mean blood loss was 1299 (range 200–4000) ml. Histological examination of the excised livers in children with FHF showed massive or submassive hepatocellular necrosis and/or cell dropout and a variable degree of mixed inflammatory cell infiltrates. In children with LOHF the livers showed, in addition, centrilobular cholestasis and hepatocyte regeneration with early nodule formation.

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Table 1 *Clinical and biochemical data of 12 children receiving transplants*

Patient no.	Type of hepatic failure	Sex	Age (months)	Diagnosis	Bilirubin (mmol/l)	ASAT (units/l)	Creatinine (mmol/l)	Prothrombin time (s)	Encephalopathy grade	Ascites
1	FHF	F	72	Carbamazepine hepatotoxicity	287	946	46	76	III	Yes
2	FHF	F	24	Carbamazepine hepatotoxicity	87	6000	91	87	III	Yes
3	FHF	M	48	Non-A non-B hepatitis	370	638	51	32	III	No
4	FHF	M	132	Non-A non-B hepatitis	632	776	106	104	IV	Yes
5	FHF	M	144	Hepatitis A	507	1325	107	63	III	No
6	FHF	F	36	Hepatitis A	339	4000	67	50	III	No
7	FHF	F	1	Haemochromatosis	212	26	22	40	II	Yes
8	LOHF	F	84	Non-A non-B hepatitis	555	465	81	33	II	No
9	LOHF	M	12	Autoimmune hepatitis	389	144	62	48	II	Yes
10	LOHF	M	168	Non-A non-B hepatitis	609	301	70	27	II	No
11	LOHF	F	24	Non-A non-B hepatitis	433	1250	55	76	IV	Yes
12	LOHF	M	1	Non-A non-B hepatitis	498	828	27	130	II	No

FHF, fulminant hepatic failure; LOHF, late-onset hepatic failure; ASAT, aspartate aminotransferase

Table 2 *Graft type and postoperative complications in 12 children receiving transplants*

Patient no.	ABO group		Graft type*	Technical complications	Infective or other complications	Outcome
	Donor	Recipient				
1	O	AB	II, III, IV		GVHD CMV infection	Died
2	A	O	Full size		Acute rejection	Alive
3	A	A	II, III			Alive
4	O	A	II, III, IV	Intra-abdominal bleeding	GVHD Cholangitis CMV infection	Died
5	O	B	Full size			Alive
6	O	O	II, III, IV		Pneumonia Acute rejection	Alive
7	O	A	II, III, IV	Portal vein thrombosis		Died
8	O	O	II, III	Intra-abdominal bleeding Biliary obstruction	Pneumonia Candidiasis	Alive
8†	O	O	II, III		Subhepatic abscess Acute rejection	Alive
9	O	O	II, III, IV	Portal vein thrombosis	Brain aspergilloma Acute rejection	Died
10	A	A	Full size			Alive
11	A	O	II, III, IV		Pneumonia Candidiasis	Alive
12	O	O	II, III			Alive

GVHD, graft *versus* host disease; CMV, cytomegalovirus, *hepatic segments according to Couinaud; †retransplantation

Children were managed in the intensive care unit for 3–30 (mean 12) days. Complications after surgery developed in eight; acute rejection occurred in four. Abdominal bleeding was a problem in two children, one of whom required laparotomy. Portal vein thrombosis was diagnosed in two, of whom one underwent successful thrombectomy 15 days after the transplant and one had infarction of the liver and died waiting for another graft. Ten infective complications occurred in seven children. Fungal infection was recognized in three (two had disseminated candidiasis that responded to treatment with intravenous antifungal agents and one had cerebral aspergillosis that did not respond). Two children presented with disseminated cytomegalovirus (CMV) infection. Bacterial infections included pneumonia in three children, cholangitis in one and subhepatic abscess in one (*Table 2*).

Four children died. Two developed graft *versus* host disease (GVHD) and were treated with high doses of steroids, antilymphocytic globulin and thalidomide; in both cases disseminated CMV infection was detected leading to death despite the treatment with anti-GHVD therapy and ganciclovir. One child died from cerebral aspergillosis and another from infarction of the graft after portal vein thrombosis

The mean length of hospital stay was 66 (range 25–260) days. Eight of the 12 children receiving transplants are currently alive, four with FHF and four with LOHF. The median follow-up was 18 months (range 3 months to 3 years). Neurological recovery in the survivors was complete. All have adequate graft function with normal liver function test results.

Discussion

The criteria for selecting children with FHF or LOHF who are suitable for liver transplantation remain difficult. The decision has to be taken before the development of major complications, particularly severe cerebral oedema and sepsis. The decision to transplant was taken in these children with the assistance of the King's College criteria[13], which depend on five variables: age <10 or >40 years; aetiology (non-A non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions); duration of jaundice before onset of encephalopathy >7 days; prothrombin time prolongation >50 s; and serum bilirubin level >300 mmol/l. Using these criteria it has been shown that in patients with more than three prognostic factors the mortality rate without transplantation approaches 95 per cent. Criteria for LOHF have not yet been developed; in the present cases the decision to transplant was taken if the patients presented with severe abnormalities in liver function test results, deep jaundice, ascites, or if there was an imminent risk of developing late complications of liver failure.

Coagulopathy should be corrected before transplantation by the administration of fresh frozen plasma, cryoprecipitate, platelets and exchange transfusions. If clinical signs of cerebral oedema are detected, the insertion of an extradural intracranial pressure monitor is advisable[13]. Monitoring of intracranial pressure is the best guide for the management of episodes of cerebral oedema. Such episodes may be successfully treated by hyperventilation and hyperosmolar mannitol and thiopentone infusions. Hypoglycaemia should be avoided by increasing the amounts of intravenous dextrose.

The lack of suitable paediatric donor livers makes the use of reduced-size and ABO-incompatible grafts necessary. Nine of the present children underwent transplantation with reduced-size grafts. It has been shown by others[14] that graft and patient survival are the same for full-size and reduced-size grafts. Morbidity and, particularly, intraoperative blood loss increase in the presence of severe coagulopathy and reduced-size grafts. However, the coagulopathy can usually be controlled. Two ABO-incompatible grafts were used; such grafts have previously been associated with an increased incidence of severe rejection, arterial thrombosis and cholangitis[15]. In the present series no such association was found. Because of the possible complications, the use of ABO-incompatible grafts can be recommended only in emergency situations.

Several defects in immunological function have been described in patients with FHF[16–18]. These defects, together with the use of invasive monitoring, immunosuppression, broad-spectrum antibiotics and treatment for graft rejection, render the child highly susceptible to bacterial and fungal infection[19,20]. Susceptibility appears to be reduced by the use of selective bowel decontamination using antibiotics and antifungal agents[21]. If sepsis is suspected, aggressive use of antibiotics and antifungal agents is recommended.

GVHD is rarely seen after liver transplantation in adults and few cases have been reported[22,23]. Two of the present 12 patients developed GVHD and both had received reduced-size livers from an adult donor. Several factors may have been involved in the development of GVHD in these children. A relatively large pool of immunologically competent cells (from the porta hepatis) is grafted in a small host with defective immunological function that makes them incapable of mounting an effective response against transplanted lymphocytes. The results of treatment with cyclosporin A, increased doses of steroids, antilymphocyte globulin and thalidomide proved disappointing. FK506 has been reported as an effective treatment for GVHD[24]. We suggest that children with FHF receiving reduced-size grafts should undergo meticulous dissection of the liver hilum excising visible lymph nodes to try to prevent GVHD.

The survival rate obtained so far with liver transplantation is encouraging. In our experience and in other adult transplant centres the survival rate of patients with FHF and LOHF is significantly lower than that for elective cases. To improve results, early referral of these children to centres with facilities and experience in liver transplantation is desirable. Better prognostic factors need to be developed that can identify earlier children who require transplantation.

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Antihepatitis C virus status in hepatocellular carcinoma and the influence on clinicopathological findings and operative results

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Antihepatitis C virus (HCV) status was investigated in 100 patients undergoing hepatectomy for hepatocellular carcinoma (HCC) between 1980 and 1989. The clinicopathological findings and operative results, in patients with or without HCV marker, were compared retrospectively. The positivity rate of anti-HCV was 51 per cent. In this group there was a higher mean age, fewer symptoms, raised alanine aminotransferase level, higher 15-min indocyanine green clearance rate and earlier tumour stage compared with the anti-HCV negative group. Positive tumour margins and vascular invasion were seen less frequently in the anti-HCV positive group. HCC with HCV marker showed characteristic features of chronic non-A non-B hepatitis and of HCC originating from liver cirrhosis. There was a better cumulative 1-year survival rate for anti-HCV positive patients, but 3- and 5-year survival rates after hepatectomy were similar in both groups. Although HCV-related HCC had typical features of chronic non-A non-B hepatitis and a relatively early stage of tumour, biological features and operative results were similar with or without the HCV marker.

The recent cloning of hepatitis C virus (HCV) DNA and the development of a specific assay for HCV have facilitated serological analyses of the relationship of this virus to non-A non-B hepatitis, chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC)[1–3]. About 70–80 per cent of cases of non-A non-B hepatitis are related to HCV, and HCV-related non-A non-B hepatitis may be the causative agent of a sequential progress from acute to chronic hepatitis, cirrhosis and HCC[4–6]. Epidemiological data indicate that the positivity rates of HCV among patients with HCC range from 29 to 75 per cent[7–10].

There is little documentation of clinical and pathological studies of HCV-related HCC with regard to the results of surgery[11]. Such investigations are required to elucidate the characteristics of HCV-related HCC in an attempt to improve the results of current therapeutic treatments for this carcinoma. In a retrospective study the anti-HCV status was examined in patients who had undergone hepatectomy and compared with clinicopathological findings and operative results.

Patients and methods

A total of 100 consecutive patients underwent hepatic resection for HCC between June 1980 and August 1989. The mean(s.d.) age was 57·0 (9·9) (range 27–81) years and the male·female ratio 83·17 Patients were classified according to Child's grade as: A, 71; B, 26; and C, three. The mean(s.d.) 15-min indocyanine green clearance rate ($ICGR_{15}$) was 19·4(12·0) (range 1–67) per cent Albumin, total bilirubin, alanine aminotransferase (ALAT) and alpha fetoprotein (AFP) levels were measured using standard laboratory methods. Liver cirrhosis was diagnosed using the criteria of Anthony *et al* [12] and was present in 61 patients. Macroscopic Eggel's classification was nodular HCC in 75 patients, massive in 22 and diffuse in three Histological features of the tumours were assessed by the criteria of the World Health Organization[13] and Edmondson and Steiner[14]. Tumour stage was classified on the tumour node metastasis (TNM/pTNM) system (*Table 1*)[15,16]. Stage I included 18 patients, stage II 33, stage III 39 and stage IV ten A tumour-free margin required 1 cm or more of resected macroscopic tumour-free tissue. Vascular invasion involving the branch of the portal and/or hepatic vein and intrahepatic metastasis was examined macroscopically and confirmed microscopically

Anti-HCV status was determined using an enzyme-linked immunosorbent assay kit (Ortho; Raritan, New Jersey, USA) on sera stored before operation. The sera were kept frozen at −70°C until tested, the cut-off value was 0·435. Fifty-one patients were positive for anti-HCV and 49 negative.

Table 1 *Tumour staging of hepatocellular carcinoma according to the tumour node metastasis classification*

Stage	Classification		
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	T_{1-3}	N_1	M_0
IV	T_4	$N_{0/1}$	M_0
	T_{1-4}	$N_{0/1}$	M_1

Details of classification

T_1	Single tumour ≤2 cm in diameter without vascular invasion
T_2	Single tumour ≤2 cm in diameter with vascular invasion or multiple tumours ≤2 cm without vascular invasion that are confined to one lobe or single tumour >2 cm without vascular invasion
T_3	Single tumour >2 cm in diameter with vascular invasion or multiple tumours ≤2 cm with vascular invasion that are confined to one lobe or multiple tumours >2 cm with or without vascular invasion that are confined to one lobe
T_4	Multiple tumours in more than one lobe or tumour(s) that involve(s) a major branch of the portal or hepatic vein(s)
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
M_0	No distant metastasis
M_1	Distant metastasis

Patients were followed every 1 to 3 months with AFP determination, liver function tests, chest radiography and ultrasonography or computed tomography. If recurrence was suspected the patient underwent angiography and treatment involving reoperation, transcatheter arterial embolization or chemotherapy.

Statistical analysis used Student's t test with Welch's correction and χ^2 test. The Kaplan–Meier method was used to estimate the survival pattern and the generalized Wilcoxon test employed to compare survival curves. $P < 0·05$ was considered significant.

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Results

Comparison of the preoperative clinical findings with or without HCV marker is shown in *Table 2*. Anti-HCV positive patients had a higher mean age, fewer symptoms and a lower positivity rate for hepatitis B surface antigen (HBsAg) compared with anti-HCV negative patients. Preoperative levels of ALAT and $ICGR_{15}$ in the former group were significantly higher compared with the latter. There was no significant difference in Child's grading between the groups. Positivity rate of hepatitis B surface antibody, AFP levels and a history of blood transfusion showed no significant differences. HCC was found on prospective follow-up screening in 44 patients (86 per cent) in the anti-HCV positive group and in 27 (55 per cent) in the anti-HCV negative group ($P < 0·01$).

Comparisons of operative and pathological findings in relation to HCV marker are shown in *Tables 3* and *4*. Macroscopic Eggel's classification showed a similar distribution between both groups and a fibrous capsule was also detected in 70 of the 75 patients with the nodular type of HCC. Tumour size in anti-HCV positive patients was significantly less than in the anti-HCV negative group ($P < 0·05$). The former had significantly earlier stages of the disease ($P < 0·05$). There were no significant differences in type of surgery carried out and the mean resected liver volume. Combined liver cirrhosis tended to be more frequent in the anti-HCV positive group but with no statistical significance. In this group the incidence of tumour-free margins was higher and vascular invasion less compared with findings in anti-HCV negative patients. There was no significant difference between the groups concerning intrahepatic metastasis. Histological features (*Table 4*) showed a similar distribution between groups, for which 78 of 100 tissue sections were selected for detailed analysis.

Table 2 *Clinical data on 100 patients with hepatocellular carcinoma in relation to hepatitis C virus marker status*

	Anti-HCV positive	Anti-HCV negative	*P*
No. of patients	51	49	
Sex ratio (M:F)	43.8	40:9	
Mean(s.d.) age (years)	59·7(7·9)	54·1(10·6)	<0·01
Symptom-free	37	25	<0·05
History of blood transfusion	16	8	
HBsAg positive	3	24	<0·01
HBsAb positive	20	11	
Mean(s.d.) AFP (ng/ml)	1560(4303)	4229(12616)	
Mean(s.d.) ALAT (units/l)	64·2(37·6)	39·2(27·8)	<0·01
Mean(s.d.) $ICGR_{15}$ (%)	22·2(12·6)	16·5(11·4)	<0·05
Child's grade			
A	34	37	
B	15	11	
C	2	1	

HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; AFP, alpha fetoprotein, ALAT, alanine aminotransferase; $ICGR_{15}$, 15-min indocyanine green clearance rate

Table 3 *Intraoperative clinical and pathological data in relation to hepatitis C virus marker status*

	Anti-HCV positive ($n = 51$)	Anti-HCV negative ($n = 49$)	*P*
Hepatectomy			
Lobectomy	11	12	
Segmentectomy	12	15	
Subsegmentectomy	20	17	
Local resection	8	5	
Mean(s.d.) resected liver volume (cm^3)	254·3(208·1)	317·0(300·0)	
Combined liver cirrhosis	35	26	
Mean(s.d.) tumour size (cm)	3·6(1·9)	5·3(3·6)	<0·05
TNM stage			
I	10	8	<0·05
II	21	12	
III	15	24	
IV	5	5	
Tumour-free margin	25	12	<0·05
Vascular invasion	11	20	<0·05
Intrahepatic metastasis	23	27	

HCV, hepatitis C virus, TNM, tumour node metastasis

Table 4 *Microscopic features of tumour in relation to hepatitis C virus marker status*

	Anti-HCV positive ($n = 40$)	Anti-HCV negative ($n = 38$)
Histological type		
Trabecular	24	30
Pseudoglandular	3	0
Compact	12	8
Scirrhous	1	0
Edmondson–Steiner grade		
I	6	2
II	28	30
III	5	6
IV	1	0

HCV, hepatitis C virus

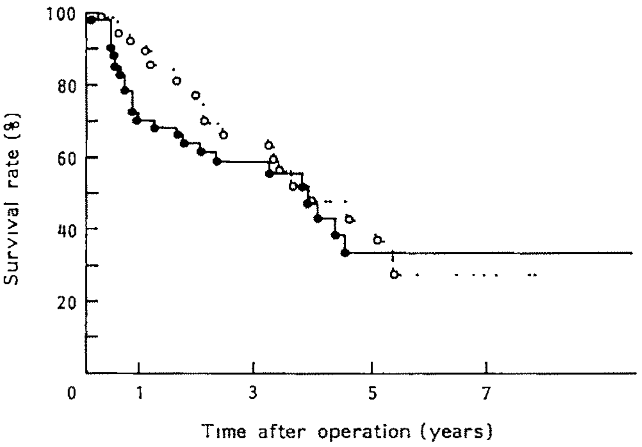

Figure 1 *Survival curves of antihepatitis C virus positive* (o, n = *49) and negative* (●, n = *47) patients, excluding operative deaths. There was a statistically significant difference in the cumulative survival rate at 1 year* (*Kaplan–Meier test*)

Twenty-five patients in the anti-HCV positive group and 26 in the anti-HCV negative group died by the end of December 1990. Each group included two operative deaths. Cumulative survival rates (*Figure 1*) of all patients except these four were 82 per cent at 1 year, 65 per cent at 3 years and 41 per cent at 5 years. Significant differences between the survival rates were seen at 1 year but not in the 3- and 5-year survivors. There were 26 survivors in the anti-HCV positive group and 23 in the anti-HCV negative group, and 11 and nine, respectively, showed recurrence. Total recurrence rates in both groups were 67 per cent and 69 per cent, respectively.

Discussion

Epidemiological studies have shown a decline in the positivity rate for HBsAg among patients with HCC, especially in Japan[3,17,18]. There is an increasing incidence of HCC associated with HCV[3–5,17,18]. In this study, the positivity rate of anti-HCV was 51 per cent and that of HBsAg 27 per cent. Recent reports from Asian and Western countries have shown a similar high frequency of anti-HCV in patients with HCC[7–9,10,18]. HCV hepatitis accounts for about 80 per cent or more of all post-transfusion hepatitis[4,5,8,10,18]. There was, however, no significant difference with regard to previous history of blood transfusion in the present series, in patients with or without the HCV marker, a finding in accord with data in earlier reports[4,5].

Factors of HBV infection, type of cirrhosis, and some environmental factors may account for the geographical distribution, as well as the different clinicopathological characteristics of HCC, including operative results[19–21]. The HCV assay system may explain some of these differences in HCC, such as those seen in Asian and Western countries[11,20,21]. Okuda *et al.* reported a significant difference in mean age at diagnosis of HCC and in AFP levels. They suggested that most patients negative for HBsAg have a related chronic non-A non-B hepatitis, as noted in a study of 113 non-alcoholic patients with histologically proven HCC in Japan[17]. Investigators in Western countries have reported conflicting findings for mean age and AFP levels in those with HCC[11,22] In the present study, anti-HCV positive patients had a significantly higher mean age, fewer symptoms, a raised level of ALAT and higher $ICGR_{15}$ compared with the anti-HCV negative patients. In addition to the higher mean age, a more active inflammatory change and a more reduced functional liver capacity were present in the anti-HCV positive patients. These findings are typical features of chronic non-A non-B hepatitis[6] and such characteristics in the anti-HCV positive patients remain after the development of HCC.

Although there was no significant difference between groups with regard to histological features, the anti-HCV positive patients had smaller tumours that were of earlier clinical stage Most of the HCC tumours, with or without HCV marker, in this series were nodular and encapsulated, lesions known for slower growth and which are often present in patients with advanced liver cirrhosis[23,24]. Chronic HBV infection is not necessarily an important cause of cirrhosis and the frequency of cirrhosis associated with HBV infection and HCC varies with geographical regions[21,22]. Nineteen (70 per cent) of 27 patients in this series positive for HBsAg had a combined cirrhosis, a frequency similar to that seen in anti-HCV positive patients. There was no significant difference in the frequency of the combined cirrhosis in this series with or without the HCV marker. Nevertheless, since functional liver capacity correlates with the severity of cirrhosis[25], the significantly reduced capacity seen in the anti-HCV positive group may indicate a more advanced stage of cirrhosis. HCCs with HCV marker may have more specific characteristics of liver cirrhosis-derived HCCs and a less advanced stage at the diagnosis of HCC than do those without the HCV marker. Prospective follow-up screening in the anti-HCV positive group may also contribute to the early diagnosis. These findings in turn contribute to the limited resection within the reserve capacity of the impaired liver, as in previous studies[24,25].

Curative resection of HCC is the treatment most likely to result in complete remission[26–29]. A tumour-free margin of 1 cm or more is a requirement for curative resection in any stage[15,30] A tumour-free margin of the resected liver was seen more frequently in the anti-HCV positive group. Although the anti-HCV positive group had a higher cumulative 1-year survival rate, the long-term survival rates at 3 and 5 years did not differ and there was no difference in the total recurrence rates, with or without the HCV marker. Therefore, an adequate tumour margin is not necessarily important for recurrence because most of the resected tumours were encapsulated and tumour tissues were not present in the inadequately resected margin[23,31].

Higher recurrence rates after hepatectomy are caused mostly by residual intrahepatic metastasis via the portal system[23,24,32]. Vascular invasion and intrahepatic metastasis are the most important biological characteristics of HCC and presumably related to tumour recurrences[33,34]. Since the rate of vascular invasion was lower in anti-HCV positive patients, similar recurrence rates in both groups are probably the result of a similar rate of intrahepatic metastasis. Certainly, in patients without vascular invasion, the multifocal type of HCC may be concerned with this higher rate of recurrence[31,35]. Biological and pathological studies will be needed to confirm this postulate[35].

In conclusion, although HCV-related HCC showed features typical of chronic non-A non-B hepatitis and a relatively earlier tumour stage, the biological characteristics and operative results are similar with or without the HCV·marker

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Vasomotor phenomena caused by histamine release from a hepatic haemangioendothelioma

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The resection of tumours that secrete metabolically active products and hormones may be complicated by the systemic release of these agents at operation. Assessment of the secretory state of the tumour and complete metabolic and hormone control must be achieved before operation. A unique liver tumour that caused episodic flushing due to the release of histamine, thus mimicking the carcinoid syndrome, is described.

Case report

A 62-year-old man presented with an 8-week history of diarrhoea and recent epigastric pain. On examination there was massive hepatomegaly Ultrasonography showed a cystic lesion in the right liver A biopsy, taken at laparoscopy, was reported as consistent with fibrosarcoma. The patient was referred for hepatic resection. On arrival the patient volunteered that he had recently suffered from hot flushing attacks. Further investigations failed to reveal a primary tumour elsewhere, and the carcinoid syndrome was excluded. Reappraisal of the original histology result suggested a mast cell tumour of low grade, plasma tryptase and methylhistamine levels were therefore measured. Computed tomography confirmed a large tumour in the right lobe of the liver with a fine plane separating the vena cava (*Figure 1*).

Treatment with H_1/H_2 blockers was commenced. The somatostatin analogue octreotide was used to block the release of vasoactive agents from the tumour. At operation a plane was established between the tumour and the vena cava, and a right hepatectomy was undertaken. There was no haemodynamic lability, indicating adequate blockade Macroscopic examination of the tumour showed a well circumscribed bosselated mass 26 cm in diameter with extensive haemorrhagic cystic degeneration. The minimum resection margin was 2 mm. Although studies on light microscopy suggested that the neoplasm had histological features of a mast cell tumour, the final diagnosis after electron microscopy was of a histamine-secreting haemangioendothelioma with reactive mast cell activity The resection margins were histologically clear. Preoperative and postoperative tryptase and methylhistamine levels were later obtained (*Table 1*). The patient is well, with normal plasma and urinary methylhistamine levels, 1 year after treatment.

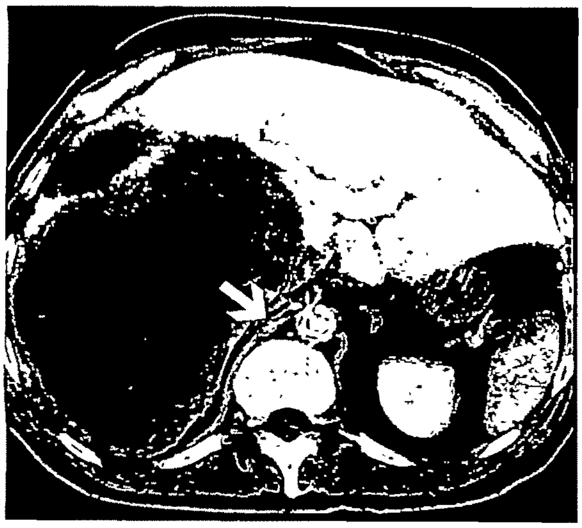

Figure 1 *Computed tomography showing a mass occupying the right liver. A fine plane is evident between the mass in the liver and inferior vena cava (arrow). Development of this plane allowed the lesion to be resected at right hepatectomy*

Table 1 *Plasma tryptase, plasma methylhistamine and urinary methylhistamine levels before and after resection of the primary tumour*

Relation to surgery	Plasma tryptase (ng/ml)*	Plasma methylhistamine (ng/ml)†	Urinary methylhistamine (ng/ml)†
5 days before	1·1	638	30
2 days after	1·1	13	—
7 days after	1·1	9	—
10 days after	1·1	25	223
1 year after	1·1	<1	<1

Normal levels: *0·5–2 ng/ml; † <1 ng/ml

Discussion

Hepatic haemangioendothelioma, first reported by Fukayama *et al.*[1], is a rare vascular primary liver tumour, the course of which is much less malignant than that of hepatic angiosarcoma[2]. The endothelial nature of this tumour was established on the basis of ultrastructural characteristics and the demonstration of factor VIII-related antigen[2]. The name 'epithelioid haemangioendothelioma' was applied by Weiss and Enzinger[3] in 1982 to emphasize the histological resemblance to epithelial neoplasms. Cellular pleomorphism, together with the parenchymal and stromal reactions, often leads to difficulties in histological interpretation and the lesion may be confused with sarcomas and secondary carcinoma.

The release of histamine occurs during the generalized degranulation of basophils within the circulation or during the degranulation of mast cells within an organ such as the skin or lung. Extensive systemic liberation of histamine can lead to anaphylaxis, but release in smaller amounts leads to flushing, urticaria etc. The half-life of plasma histamine[4] is 2–3 min, precluding accurate measurement. Histamine is methylated in the liver and methylhistamine has a substantially longer half-life[4]. Both plasma and urinary methylhistamine levels[5] can now be assayed. In addition tryptase, a neutral protease, is released when mast cells degranulate and its levels in plasma can now be measured as an index of mast cell activation[6].

Two explanations are possible for the normal tryptase levels in this patient. First, tryptase released in an organ such as the liver may be fixed before it can appear in the systemic circulation. Second, a haemangioendothelioma with mast cell reactivity may not behave like a true mast cell tumour and may have much lower levels of tryptase.

The clinical course of epithelioid haemangioendothelioma reported in the literature has varied[2] between death from liver failure within months and survival for many years. Although chemotherapy and radiotherapy have been ineffective, orthotopic liver transplantation has been successful in several patients with extensive parenchymal replacement and absence of extrahepatic disease[2].

The release of histamine from this particular tumour has never been documented: perhaps patients with vasomotor symptoms and otherwise negative investigations should undergo urinary and plasma methylhistamine assays as part of initial examination. The identification of such a primary tumour affords the patient a chance of lasting remission provided that the neoplasm is adequately treated by hepatic resection or even

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transplantation. Furthermore, the identification of recurrent disease at follow-up might be facilitated by assessment of serial methylhistamine levels.

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Intussusception as a cause of postoperative intestinal obstruction in children

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Intussusception is an uncommon cause of postoperative intestinal obstruction. Two patients are discussed who developed intussusception, following nephrectomy for Wilms' tumour in one and a Duhamel pull-through procedure in the other. Manual reduction was successful in the first patient, but resection of the intussusception was necessary in the second.

Case reports

Patient 1

A 3-year-old boy underwent left nephrectomy for Wilms' tumour He was commenced on oral fluids and given mebendazole (100 mg twice a day for 3 days) for ascariasis After 11 days the child started to vomit and developed abdominal distension, plain radiography suggested small bowel obstruction. Nasogastric suction and intravenous fluids gave no improvement and laparotomy showed an ileoileal intussusception This was manually reduced.

Patient 2

An 11-month-old infant underwent Duhamel's procedure with colostomy for Hirschsprung's disease. Oral fluids were commenced on day 3, but 2 days later the patient developed abdominal distension and wound dehiscence, which was repaired Distension persisted and plain abdominal radiography suggested intestinal obstruction. A laparotomy was undertaken 21 days after the first operation, an irreducible ileoileal intussusception was resected and end-to-end anastomosis performed.

Discussion

Intussusception accounts for 5–10 per cent of postoperative obstructions in children[1] and usually occurs within 2 weeks of surgery. Adhesive obstructions tend to develop later[1,2]. Postoperative intussusception occurs without the classical triad associated with idiopathic invagination but does involve bilious vomiting or increased nasogastric aspiration of bilious material, and abdominal distension after the return of gastrointestinal function[2].

Only 3·5 per cent of postoperative intussusceptions are likely to be diagnosed before surgery[1]. Results of plain radiography are usually non-specific, suggesting small bowel obstruction; contrast studies are unrewarding as these intussusceptions usually occur in the small bowel[3]. Ultrasonography of the abdomen may help diagnosis by detecting characteristic multiple concentric rings on transverse section with a sonolucent outer layer and echogenic centre[4,5].

The aetiology of postoperative intussusception is unknown. It frequently follows intra-abdominal and retroperitoneal procedures such as nephrectomy for Wilms' tumour and pull-through operations for Hirschsprung's disease[1], and occasionally occurs following non-abdominal surgery[1,2]. Disorders of bowel motility may be implicated (for example after a Nissen fundoplication in patients with neurological disorders and motility abnormalities) or it may occur secondary to anaesthesia, local trauma and hypoxia of the bowel, electrolyte imbalance, chemotherapy or radiation[2,3]. Neuroendocrine factors and neurotransmitters may be important in patients with neural crest abnormalities such as Hirschsprung's disease[3,4]. A bolus of roundworm may have been a contributory factor in the first patient described in the present paper.

Hydrostatic reduction of postoperative intussusceptions is usually impossible because most occur in the small bowel. However, 96 per cent are amenable to manual reduction[1]. A delay in diagnosis (as in patient 2) may necessitate resection of the intussusception, with increased morbidity and mortality rates (the latter 7·6 per cent in such cases)[1].

Postoperative intussusception should be considered and ultrasonography undertaken in children who have undergone extensive intra-abdominal or retroperitoneal procedures and who show evidence of obstruction or ileus in the first 2 weeks after initial return of gastrointestinal function.

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Case report

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Intussusception associated with nephrotic syndrome

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Two children who presented with intussusception and nephrotic syndrome are described and a possible relationship between these conditions discussed.

Case reports

Patient 1

A 4-year-old girl presented with a 2-week history of colicky abdominal pain and abdominal distension. Bowel habits were normal and she had vomited once. Examination revealed a mildly wasted child with an impression of a mass in the right upper quadrant. There was no peripheral oedema and the blood pressure was raised (131/102 mmHg). Proteinuria >5 g/l was noted on dipstick testing and attributed to an intercurrent urinary tract infection. Abdominal ultrasonography revealed a complex mass with a multiple concentric ring appearance consistent with an ileocolic intussusception (*Figure 1*). There was also marked bilateral renal enlargement. The intussusception required surgical reduction without resection; no lead point was found and copious ascites was present.

After surgery the child became oliguric and oedematous with a weight gain of 1·4 kg over 4 days. Small bowel obstruction then developed and a jejunoileal intussusception was diagnosed by ultrasonography. This was reduced at a second laparotomy and again the bowel appeared macroscopically normal.

The nephrotic syndrome persisted; percutaneous renal biopsy 11 days after admission showed the features of minimal change glomerulonephritis.

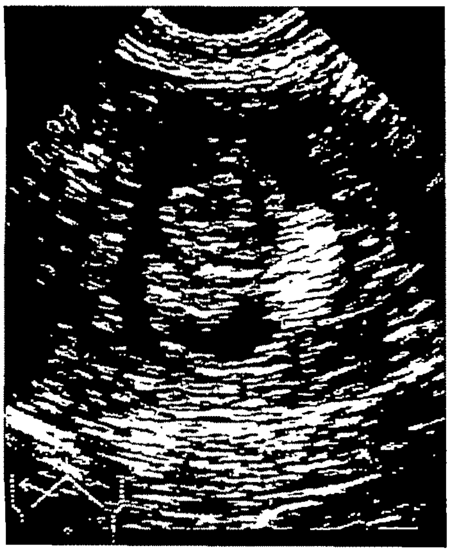

Figure 1 *Transverse ultrasonographic section of ileocolic intussusception*

Patient 2

A 6-month-old girl presented with a 1-day history of abdominal pain and bilious vomiting. Urine analysis showed proteinuria >2 g/l. Abdominal radiography revealed small bowel obstruction and a barium enema confirmed the diagnosis of ileocolic intussusception. This was reduced surgically; no lead point was discovered.

After surgery the patient became markedly oedematous (weight gain of 1 kg), hypertensive (140/65 mmHg) and hypoalbuminaemic (13 g/l). Chromosome analysis, undertaken because of the young age of onset of nephrotic syndrome, showed the patient to be genotypically 46XY although she had normal female external genitalia. This finding was suggestive of Drash syndrome, which has a predisposition to Wilms' tumour and to diffuse mesangial sclerosis[1]. This latter change was demonstrated in the patient on renal biopsy.

Discussion

Both children presented with proteinuria, but the significance of this was not appreciated until after operation, when they developed florid signs of nephrotic syndrome: oedema, hypoalbuminaemia, oliguria and hypertension.

The oedema of nephrotic syndrome is present throughout the body; in the bowel wall and mucosa it is known to cause disturbances of gastrointestinal function, including motility[2]. Reymond proposed a 'pivot (lead point) and torque' theory for development of an intussusception[3]. We propose that a combination of patches of bowel wall oedema and peristaltic incoordination[4] could have provided the pivot and torque in the patients described.

An association between nephrotic syndrome and intussusception has been recorded only once before[5], in which case the intussusception was attributed not to the nephrotic syndrome but to an intramural haematoma acting as the lead point. The patients described in this paper had no macroscopic lesions to act as lead points.

In conclusion, nephrotic syndrome in children may evolve slowly and attention should be paid to the results of urine analysis of any surgical patient. Conversely, intussusception should be included in the differential diagnosis of any child with nephrotic syndrome who presents with abdominal pain and in whom peritonitis is suspected. Ultrasonography was found to be of immediate help in diagnosis.

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Toxic dilatation of the colon in Chagas' disease

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Toxic megacolon occurs in colitis of differing aetiology. This report describes 15 patients with chagasic megacolon with this complication. The clinical signs and symptoms in all patients were pain and progressive abdominal distension accompanied by fever, severe toxaemia and shock. Seven patients developed this clinical pattern after manual removal of faeces. The remaining patients had pain and abdominal distension followed by signs of severe toxaemia when first examined. Nine patients underwent total colectomy with ileostomy (one death), four partial colectomy (all died) and two received medical treatment (both died). At autopsy, three of the four patients undergoing partial colectomy had residual colitis and enteritis. The surgical procedure of choice for this complication of chagasic megacolon is total colectomy.

Toxic dilatation of the colon is a severe condition related to the fulminating course of several forms of colitis[1–3]. The colon loses its ability to contract and becomes dilated, distended and highly susceptible to perforation[4,5]. The clinical pattern is dramatic and frequently fatal, with rapid progression to abdominal distension, vomiting and diarrhoea, followed by severe toxaemia and circulatory collapse[4–6].

Cases of toxic dilatation of the colon in patients with chagasic megacolon were first reported[2] in 1976. In view of the medical importance of Chagas' disease in Brazil, experience with the management of toxic dilatation of the colon associated with chagasic megacolon is presented.

Patients and methods

Fifteen patients with toxic dilatation of the colon associated with chagasic megacolon diagnosed between 1975 and 1989 were studied. In this period 256 patients with chagasic megacolon underwent surgery at the University Hospital, Botucatu Medical School Thirteen patients were men; ages ranged from 32 to 72 (mean 52) years. All had a history of chronic intestinal obstipation and positive epidemiology and/or serology for Chagas' disease. The diagnosis of toxic dilatation was based on clinical, radiological and histopathological findings.

Results

Forty-five of the 256 patients with chagasic megacolon had colitis characterized by multiple ulceration; 15 of these developed toxic dilatation of the colon, giving an incidence for this complication of 5·9 per cent (*Table 1*).

The clinical findings were pain and progressive abdominal distension, fever, severe toxaemia, dehydration and shock. Leucocytosis and biochemical changes consistent with toxaemia and shock were observed in all patients. Seven presented clinical and radiological evidence of faecal impaction on presentation and were submitted to manual evacuation. Severe toxaemia ensued 24–48 h later. There was evidence of sigmoid volvulus in three patients and a history of acute diarrhoea in four. Radiography revealed distension, especially of the large bowel; pneumoperitoneum was present in two patients.

Two patients were not fit for surgery and underwent gastric and rectal decompression with antibiotic administration; both died. Nine patients underwent total and four partial colectomy The surgical findings were marked distension of the entire colon, perforations and the presence of a lemon-yellow fluid or purulent material in the peritoneal cavity. The perforations were punctate and difficult to locate.

Examination revealed confluent ulceration of the colon in all patients, usually arranged along the taeniae. The lesions were more prominent in the dilated portion of the sigmoid, but extended throughout the colon, reaching the terminal ileum in four patients In all patients the mucosa of the rectal ampulla was preserved. Histologically, there was abundant granulation tissue at the base of the ulcers and a diffuse inflammatory infiltrate reaching and dissociating the muscle layers. There was a marked decrease or absence of myenteric nerve plexuses and neurones in megacolic areas.

Table 1 *Incidence of colitis and toxic dilatation in 256 patients with chagasic megacolon, 1975–1989*

	Colitis in megacolon	Toxic dilatation in colitis	Toxic dilatation in megacolon
Cases	45 of 256	15 of 45	15 of 256
Incidence (%)	17·6	33	5·9

The four patients undergoing partial colectomy died, three on the third or fourth day after surgery with signs and symptoms of toxaemia. One died from cardiac arrhythmia. Of the nine patients undergoing total colectomy, one died during the late postoperative period from dehiscence and peritonitis. The eight surviving patients presented postoperative complications such as multiple dehiscence and peritonitis, and one developed short bowel syndrome.

Those who died were submitted to autopsy, which demonstrated the presence of residual colitis and ulcerative enteritis in three of the four patients submitted to partial colectomy.

Discussion

The incidence of toxic dilatation of the colon in Chagas' megacolon in this series is 5·9 per cent, which is just outside the 1·5–5·5 per cent range reported in idiopathic ulcerative rectocolitis[7]. Toxic dilatation may occur in any form of severe colitis[1–3,8,9]. In chagasic colopathy the onset of mucosal inflammation is thought to be secondary to modification of the intestinal flora caused by chronic faecal stasis Several patients developed toxic dilatation after manipulation for faecal emptying. The enema fluids used in cleaning the dilated loop, with its large absorptive surface and ulcerative lesions, may enhance absorption of toxins, bacterial translocation and transmural extension of inflammation.

The diagnosis of toxic dilatation is based on clinical and radiographic examination of the abdomen[9–12]. In chagasic megacolon, this complication should be suspected more on the basis of the rapidly evolving clinical picture of abdominal

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distension and severe toxaemia than on radiological monitoring. Review of abdominal radiographs did not allow identification of differences between characteristics recorded before and after the occurrence of toxic dilatation. In patients with sigmoid volvulus there was no improvement in abdominal distension after endoscopic manipulation and decompression of the colon. The general condition of the patients became markedly worse after manipulation and they probably already had toxic dilatation. Sixty per cent of the patients had multiple perforations in the resected colonic segment but radiography revealed pneumoperitoneum in only two.

Patients with chagasic megacolon are usually in a poor nutritional state with a consequent altered response to stress. This may explain apparent clinical stabilization despite severe toxaemia. White cell counts may be an important parameter, especially if they follow the haematological findings of patients with mesenteric thrombosis.

Proctocolectomy with ileostomy, partial colectomy with ileostomy, and ileostomy with endoscopic decompression are used for patients with toxic dilatation. Each procedure has advantages and disadvantages[8,9,12–14]. In chagasic megacolon the colitis does not affect the rectal ampulla and permits total colectomy without rectal excision. Most deaths occurred in patients submitted to partial colectomy, and necropsy showed the presence of residual colitis and enteritis. Total colectomy with ileostomy is the surgical procedure of choice in toxic dilatation of chagasic megacolon. When this dramatic complication is suspected, early surgery is imperative.

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Rectal cancer risk in older patients with familial adenomatous polyposis and an ileorectal anastomosis: a cause for concern

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The risk of rectal cancer in 224 patients with familial adenomatous polyposis with an ileorectal anastomosis has been estimated by life-table analysis. Until the age of 50 years the cumulative risk is reasonably low at 10 per cent (95 per cent confidence interval 4·5–16 per cent), increasing sharply to 29 per cent (95 per cent confidence interval 18–40 per cent) by the age of 60 years. This means that surveillance of the retained rectum in older patients must either be improved or they should undergo restorative proctocolectomy in earlier middle age.

Controversy exists as to whether proctocolectomy and pouch formation or total colectomy and ileorectal anastomosis (IRA) is the best prophylactic operation for patients with familial adenomatous polyposis (FAP). Protagonists of the former procedure argue that the risk of colorectal cancer is abolished and the functional result compares well with an IRA[1]. Protagonists of colectomy and IRA argue that pouch surgery has more frequent and more severe perioperative complications than IRA[2], important when considering the impact on the willingness of other family members to attend for screening and surgery, and that the greatest risk of death from cancer lies with the upper gastrointestinal tract[3].

Some workers have attempted a discretionary policy: where the subsequent risk of cancer is perceived to be high (older age at time of operation, dense rectal polyps, family history of rectal cancer) a pouch has been chosen; otherwise an IRA is performed. This study examined the cumulative probability of rectal cancer following IRA in patients with FAP by life-table analysis to determine which factors predict subsequent development of rectal cancer and to establish whether patients with an IRA should at some time have the rectum removed or the frequency of surveillance increased.

Patients and methods

Patients selected for the study were all those on the St Mark's Polyposis Registry whose IRA was performed at St Mark's Hospital for histologically proven FAP. Between 1948 and the end of 1990, 222 patients had IRA performed as a primary procedure for polyposis and two following previous operation for colonic lesions at other hospitals Any patient presenting for IRA who was found to have rectal cancer at the time of operation underwent definitive proctocolectomy and end ileostomy or restorative proctocolectomy (RPC) and was therefore not included in the study. A patient was not considered to have cancer until there was unequivocal histological evidence of invasive adenocarcinoma.

The length of follow-up after IRA was 1–43 years; to maximize the use of follow-up years in this population a life-table analysis was performed. A patient was included for analysis until death ($n=44$), removal of the rectum for uncontrollable polyps or at the patient's request ($n=14$), diagnosis of rectal cancer ($n=22$) or until 30 November 1991 ($n=144$).

Results

Cancer of the rectum following IRA developed in 22 patients whose details are shown in *Table 1*. Fifteen patients were male and seven female ($P=0·18$, binomial comparison of proportions). Comparing 5-year age groups, more cancers developed in those between 55 and 60 years of age, but because of a few younger patients, the mean age of development of rectal cancer was 48·3 (range 28–67) years. The mean length of time after IRA was 13·5 (range 1–37) years. Nine of these patients have subsequently died, five from rectal cancer and two from upper gastrointestinal tumours. Of the other two patients, one died from a blood transfusion reaction and the other committed suicide. The 5-year survival rate by life-table analysis following the diagnosis of rectal cancer in this group

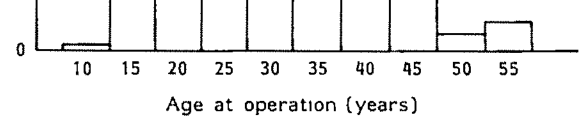

Figure 1 *Age at ileorectal anastomosis*

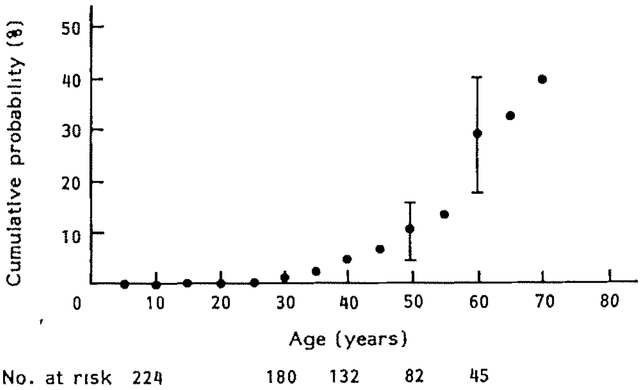

Figure 2 *Cumulative probability of developing rectal cancer Bars are 95 per cent confidence intervals. Comparison of risk up to 50 years with after this age is clinically and statistically significant*

Presented to the Surgical Research Society in London, UK, January 1992 and published in abstract form as Br J Surg *1992; 79 A460*

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Table 1 *Details of patients with familial adenomatous polyposis developing rectal cancer*

Patient no.	Sex	Age at IRA (years)	Age at cancer (years)	Cancer in colon specimen	Symptoms	Last seen (months)	Dukes' classification
1	M	18	28	No	n.k.	n.k.	A
2	F	16	34	No	Yes	<12	B
3	F	33	35	Yes	Yes	<6	A
4	M	25	38	No	No	>24	C
5	M	27	38	Yes	Yes	<24	B
6	F	14	39	No	No	<6	A
7	M	33	41	No	n k	n.k.	C
8	M	33	41	No	No	<6	A/C
9	M	40	46	No	Yes	<24	A
10	M	43	46	No	No	<6	A
11	M	42	48	No	n.k.	n.k.	B
12	M	50	51	No	No	<6	C
13	M	44	52	Yes	Yes	<12	C
14	F	53	56	No	No	<6	C
15	M	30	56	No	No	<6	A
16	M	38	56	No	No	<6	C
17	M	26	56	No	Yes	<6	Polyp
18	M	48	57	No	Yes	<6	A
19	F	25	58	No	No	<6	C
20	F	21	58	Yes	No	<6	B
21	M	40	61	No	No	<6	C
22	F	65	67	Yes	No	<6	A

IRA, ileorectal anastomosis; n.k., not known

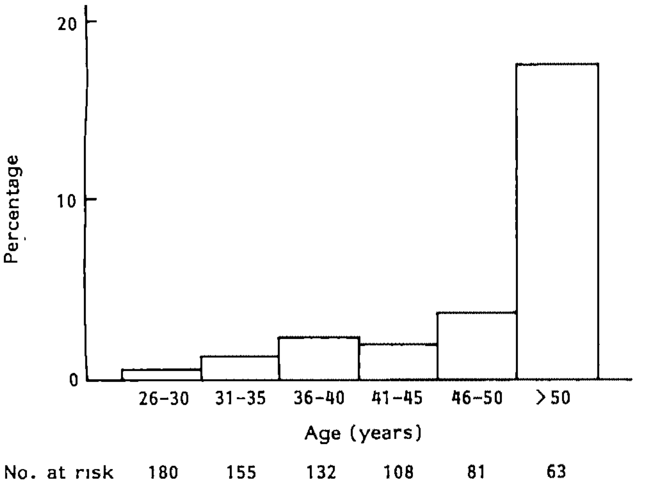

Figure 3 *Proportion of patients with rectal cancer. A clinically significant increase in risk after 50 years is present*

of patients is 78 per cent (95 per cent confidence interval (c.i.) 58–98 per cent). Death from disseminated rectal cancer was used as the endpoint; those dying from other causes have been removed from the total number at risk in the following time interval.

Of the 22 patients, information on symptoms was available in 19. Only seven patients were known to be symptomatic at the time of presentation with rectal cancer; of the 12 who were asymptomatic, 11 had been seen within the previous 6 months and examined by a clinician or clinical assistant of consultant level. The mean size of the rectal tumour in the asymptomatic patients was 2·1 (maximum 4) cm, yet six already had lymph node metastasis.

Figure 1 shows the distribution of age at IRA; the mean age at operation was 26 (median 24) years. The mean follow-up was 13·6 (range 1–43) years after IRA. The total follow-up was 3023 patient-years.

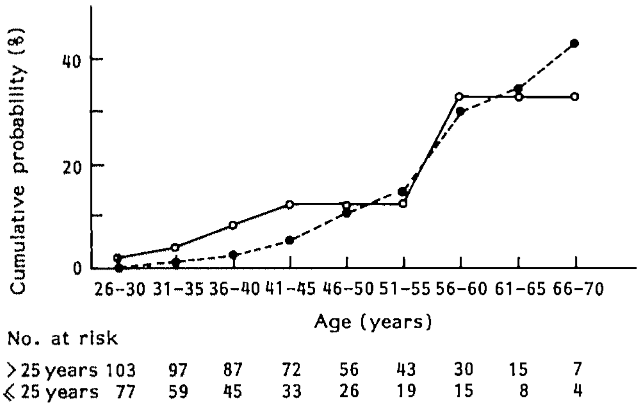

Figure 4 *Cumulative probability of developing rectal cancer dependent on age at ileorectal anastomosis* ○, *>25 years;* ●, *≤25 years. Younger patients are as likely as older ones ultimately to develop cancer* (P = 0·4, *log rank analysis*)

Figure 2 shows the probability of developing rectal cancer in patients with FAP who have undergone IRA with no evidence of rectal cancer at the time of the initial operation. The probability of rectal cancer developing by the age of 50 years is 10 per cent (95 per cent c.i. 4·5–16 per cent). The probability of rectal cancer developing by the age of 60 years is 29 per cent (95 per cent c.i. 18–40 per cent).

Figure 3 shows the percentage of patients with rectal cancer in each age group as a proportion of those at risk. It demonstrates both the low risk in patients under the age of 50 years and the sharp increase in risk thereafter.

The cumulative probability of developing rectal cancer was analysed by age at IRA, 116 patients undergoing their operation by the age of 25 years and 108 after this age. Life-table analysis was performed on each group and is shown in *Figure 4*. Log rank analysis showed age at IRA not to be a statistically significant predictor of the subsequent risk of rectal cancer ($P = 0{\cdot}4$).

Discussion

FAP is a genetically inherited disease with autosomal dominant inheritance, the gene of which is located[4] in region 21 of the long arm of chromosome 5. The familial pattern of the disease was first noted by Cripps[5] in 1882. During the past 80–90 years the growth of polyposis registry work has enabled this department to trace large numbers of 'at-risk' members of affected families and offer them screening and prophylactic surgery. Bussey[6] showed that the mean age of a patient developing cancer in a propositus group was 39 years. (A propositus group comprises patients presenting with symptoms before screening or prophylactic surgery.) However, over 15 per cent of affected patients will develop cancer by the age of 25 years and therefore operation is usually offered before the age of 20 years. Controversy has reigned between centres as to the operation of choice for prophylaxis for FAP. The three operative procedures available are: proctocolectomy and ileostomy, which is rarely used unless there is a cancer of the lower third of the rectum; RPC, which eliminates the risk of colorectal cancer but may introduce serious morbidity to a young asymptomatic group of people[7]; and colectomy with IRA. In the absence of contraindications, e.g. large numbers of rectal polyps or poor follow-up[2], total colectomy with IRA has been the procedure of choice at this centre and many others Lockhart-Mummery and colleagues in 1956 stated that IRA was preferable to proctocolectomy and ileostomy since the risk of developing carcinoma in the rectal stump was small if carefully observed and IRA avoided the need for pelvic dissection and its consequent morbidity in the young[8]. The first RPC for FAP was performed at St Mark's in 1977 by Sir Alan Parks. A recent study compared the morbidity and function with IRA or RPC. Twenty-four patients with FAP had RPC performed as the primary procedure: three had uncontrollable polyps, four had rectal cancer at presentation, five had colonic cancer, in 11 it was the surgeon's policy and in one referral was specifically for a pouch procedure. There was a significantly increased immediate and longer-term morbidity rate in patients undergoing RPC, with night evacuation in 45 per cent as opposed to 10 per cent in the IRA group, and sexual activity compromised in 33 per cent; many other factors seemed evenly balanced[7]. Patients undergoing IRA, however, required rectal surveillance at 6-monthly intervals for life.

Bussey used the propositus group to study the incidence of cancer in patients with polyposis before the introduction of IRA and found that 53·6 per cent (141 of 263) had cancer of the rectum at the time of diagnosis with a mean age of 39 years. The mean age of developing rectal cancer in this post-IRA group was 48·3 years, which compares closely with the Mayo Clinic result in 1970 (median age 48 years)[9]. In the Mayo Clinic series, 59 per cent of patients had cancer in the retained rectum by 23 years after operation (the mean age at surgery was 36 years). By 23 years after operation patients in the present study had a cumulative probability of developing rectal cancer of only 15 per cent, but the mean age at operation was 10 years earlier. It therefore appears from these results that it is the chronological age and not the number of years of follow-up that is the important risk factor. Other series have reported incidences as low as nil[10], 2·2 per cent[6] and 5·2 per cent[11], suggesting a remarkably low relative risk of rectal cancer in patients with FAP with an IRA. However, Moertel *et al.*[9] suggested that too few patients had been followed up for greater than 10 or 15 years in any of these studies, a comment which from our current data appears to be justified.

Of interest, Bussey's propositus group developed rectal cancer at a mean age of 39 years, whereas in the Mayo Clinic series and in the recent analysis in this centre the average ages were 48 and 48·3 years respectively. This finding suggests that regular review and fulguration may delay the development of rectal cancer by 10 years, or alternatively that IRA may alter the disease process, perhaps through its effect in reducing rectal mucosal proliferation after colectomy[12].

The findings in the present study suggest that the cumulative risk of developing rectal cancer below the age of 50 years is low; indeed only six patients developed such cancer by the age of 40 years. The risk appears to be age related and not dependent on the time after IRA or age at original operation. The operation of choice for FAP may remain total colectomy and IRA if the patient presents when under the age of 30 years. This minimizes the morbidity of a prophylactic operation during the young and child-bearing era. Patients presenting after this age should be offered RPC and those with an established IRA need further screening or RPC by the age of 45 years.

In the Mayo Clinic experience, the median time from last sigmoidoscopic examination to the development of cancer was 6 months, the same as the present study group. Fourteen of the present 19 patients for whom full information on screening was available had undergone surveillance within the previous 6 months. At present screening is performed using rigid sigmoidoscopy once every 6 months, or more frequently if multiple large polyps are noted. Frequency of screening or the method of screening must be changed if the rectum is to remain. Flexible videoendoscopy at fixed intervals of 4 months is now being considered for all patients at risk over the age of 45 years who wish to retain the rectum.

Acknowledgements

The authors thank Dr K Neale, the late Dr H. J R. Bussey and the Polyposis Registry for their help in providing data and also thank the surgeons under whose care the patients were or are being treated: Mr P R Hawley, Mr J. P S Thomson, Mr R. J. Nicholls and Mr J. M. A. Northover Support for this study was from the St Mark's Research Foundation.

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Surgical workshop

Br. J. Surg. 1992, Vol. 79, November, 1207–1208

Laparoscopic abdominoperineal resection of the rectum

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The enthusiasm for laparoscopy in general surgery was stimulated by the development of laparoscopic cholecystectomy[1,2], in which, apart from using a different system of visualization and some new instruments, the procedure is effectively the same as the open approach. Laparoscopic removal of the colon has been performed using either an extracorporeal resection and anastomosis or a totally intracorporeal procedure[3,4]. However, there are concerns that complete cancer resection may not be obtained or that the operative field may be soiled by faecal content. One colonic procedure that is ideally suited for the laparoscopic approach is abdominoperineal resection of the rectum, especially for benign disease. Such a case for intractable incontinence and prolapse is presented.

Surgical technique

The patient was a 63-year-old woman who suffered from calcinosis, Raynaud's phenomenon, sclerodactylia and telangiectasia (CRST syndrome), which had caused pericarditis and muscular wasting. She also had a history of two vaginal deliveries, haemorrhoidectomy and fistulectomy. The patient was referred for a chronic rectal prolapse, which was constantly descended, and severe faecal incontinence with no sensation or control. Anal manometry revealed very low resting and squeeze pressures, and pudendal nerve electromyography revealed markedly raised latencies. An attempt was made to repair the sphincter by a postanal and anterior approach, but the muscle present was minimal and the repair at the time was considered unsuccessful. Therefore, a Silastic (Dow Corning, Los Angeles, California, USA) impregnated Dacron (Du Pont, Wilmington, Delaware, USA) sheet was inserted. This contained the prolapse for a while, but eventually the prosthesis extruded through the perianal skin and all symptoms recurred. The patient's life was dominated by the situation and she requested a permanent colostomy. It seemed reasonable that resection of the rectum would ensure a cure of the prolapse and prevent a chronic mucus leak, as the anus was totally patulous.

The patient had no previous abdominal incisions and no evident hernia. Under general anaesthesia, the bladder was decompressed with a Foley catheter and the stomach with a nasogastric tube. Pneumoperitoneum was achieved to a pressure of 15 mmHg with a Veress needle, and a 30° laparoscope (Karl Storz, Tuttlingen, Germany) was inserted through the umbilicus. A 12-mm cannula (US Surgical, Norwalk, Connecticut, USA) was inserted in the right iliac fossa, one of 5 mm inserted just to the left of the xiphisternum and two 5-mm cannulas were inserted in the left iliac fossa (*Figure 1*). Through the last two cannulas, the sigmoid colon was elevated and a suitable point of division was chosen. A window was made in the mesentery via the right iliac fossa cannula, and the bowel was divided using the Endo-GIA stapler (US Surgical). The distal end of the colon was retracted towards the head via the xiphisternal cannula and elevated via the left iliac fossa portal. The mesentery was divided close to the bowel using a combination of electrocautery and clips. Once the peritoneal reflection had been reached, this was scored, and dissection of the lateral ligaments was carried out using two-handed dissection with instruments through both iliac fossa cannulas.

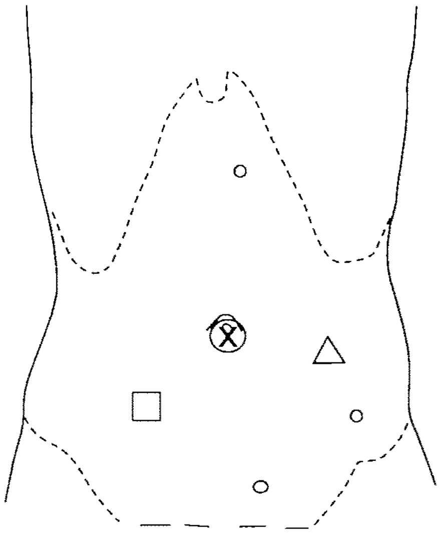

Figure 1 *Diagrammatic representation of cannula placement for laparoscopic abdominoperineal resection of the rectum.* ⊗, *11-mm cannula;* ○, *5-mm cannulas,* □, *12-mm cannula;* △, *20-mm cannula through which the colostomy was brought out*

A circle of skin 20 mm in diameter was excised at a preselected site in the left iliac fossa and through this a 20-mm trocar (Karl Storz) was introduced under direct vision. The proximal colon was grasped and the peritoneum of the mesentery was scored to ensure that the bowel was under no tension; the colon was then brought out together with the 20-mm cannula. A gas seal was attained with a petroleum jelly gauze swab placed at the colostomy site. At this juncture, the perineal dissection was started, and little was needed to complete the resection. The specimen was then withdrawn from the perineum with obvious loss of pneumoperitoneum. Two drains were placed through the perineum, which was then closed, and the pneumoperitoneum was re-established. Lavage was carried out, and total blood loss was estimated at 150 ml. All cannulas were then removed and the colostomy was completed in the usual fashion. The total operating time was 4 h 20 min. Postoperative progress was unremarkable, with pain only in the perineal wound, and bowel function returned within 2 days of operation. The patient was discharged on the fifth day after operation and had minimal constitutional upset from the procedure. She is well 4 months later.

Discussion

As laparoscopic procedures are attempted, perfected and reported, caution in their widespread application must be exercised. It has been clearly demonstrated that solid organs or the colon may be dissected laparoscopically[5], but advantages to the patient must be ensured and disease treatment must not be compromised. The most obvious example of such use would be in the management of a patient with cancer, where the principles of a wide resection must be followed. When dealing with colonic resection, no faeces should be spilt and a sound anastomosis should be achieved[6].

This report demonstrates that it is feasible to perform laparoscopic resection of the rectum. Although 4 h of operating time was needed, advantages to this very frail patient included reduced pain from wound healing, less likelihood of pulmonary complications and earlier return of bowel function and mobility. In our opinion, it would be feasible to perform a resection for cancer in similar circumstances, provided the tumour was of manageable size. Haemostasis was achieved, and a good view of the ureters was obtained.

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The move by the American Society for Colon and Rectal Surgery to form a registry of all such cases is to be commended. Future developments should receive careful and critical scrutiny.

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Announcement

European Surgical Fellowships

Since 1990 the Council of *The British Journal of Surgery* has awarded European Fellowships, each holding a value of up to £3000. Four Fellowships were awarded in 1990 and three in 1991.

In 1992 the scheme was expanded to allow surgeons working in other European countries to visit the UK. Four fellowships were awarded in that year, to Mr D. C. Mitchell (London), Mr T. H. Brown (Manchester), Dr E. M. Targarona (Barcelona) and Dr B. Nardo (Bologna)

It is Council's intention to offer European Fellowships once again in 1993. Applicants should submit details of their proposed itinerary and its anticipated costs, together with a curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK, by 1 February 1993.

D. C. Carter

Br. J. Surg. 1992, Vol. 79, November, 1209–1212

Mucin changes in ileoanal pouches monitored by metabolic labelling and histochemistry

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The pattern of mucin synthesis and secretion in mucosal biopsies from the proximal ileum, distal ileum, rectum and pouch before and after ileostomy closure was monitored in patients undergoing restorative proctocolectomy by metabolic labelling with [^{3}H]glucosamine and [^{35}S]sulphate and compared with the mucin histochemistry in each patient. Metabolic labelling clearly demonstrated a reduction in sulphation associated with the rectal mucosa in colitis. Significant differences in the turnover of isolated secreted mucin between proximal and distal ileum and rectum were also found, as was a metaplastic change towards a colonic-type mucosa in the pouch before and after ileostomy closure relative to the proximal and distal ileum, and rectum. This technique can be used to monitor colonic metaplasia in the pouch mucosa and is suitable for comparative studies where mucin changes are implicated.

Characteristic changes in the pattern of mucosal staining for mucus glycoproteins (mucins) have been described in ulcerative colitis[1] and in the pelvic ileal reservoir following restorative proctocolectomy[2]. In the pouch there is a change from small bowel-type sialomucin; villous flattening usually occurs as the mucosa takes on the colonic-type appearance[2]. These changes are probably patchy[3], but it is unclear how closely they relate to episodes of inflammation within the reservoir[4] It is probable that the pouch mucosa may need to become flat and 'colonized' before the onset of pouchitis[5]. Methods used to assess these histochemical changes are open to subjective variation and give no measure of the secreted mucin component.

Confusion exists over the practical application of the high-iron diamine–alcian blue method[6,7], but these problems may be overcome by staining large batches of slides and employing controls of ileum, stomach and right colon as a composite block with known staining characteristics. It is difficult to distinguish small amounts of sialomucin (blue) admixed with larger amounts of sulphated mucin (brown). This problem is more fundamental with the saponification–alcian blue pH 1–mild periodic acid Schiff (KOH–AB1–mPAS) technique[8,9].

An alternative method of assessment uses metabolic labelling followed by isolation of mucins[10–12]. Several different radioactive carbohydrate precursors have been used[13–17], of which glucosamine has proven the best because it is incorporated into three of the main monosaccharides found in mucins: *N*-acetylglucosamine, *N*-acetylgalactosamine and the sialic acids[10,11,13,14,18]. Incubation of biopsies in organ culture with two different radioactive precursors allows qualitative mucin differences to be determined by comparing the ratios of incorporation. Variation in the turnover of secreted and intracellular mucins can be assessed by the total amount of each isotope found in these fractions.

This study analyses the nature of mucin changes occurring in the mucosal tissue of the ileum and rectum before pouch formation, and in the pouch before and after ileostomy closure. Histological appearance and mucin histochemistry using the high-iron diamine–alcian blue[6] and phenylhydrazine PAS[19] methods were compared with radioactive incorporation into isolated mucins after metabolic labelling with [^{35}S]sulphate and [^{3}H]glucosamine.

Patients and methods

Fourteen patients (age range 21–70 years; ten men) undergoing restorative proctocolectomy with a W pouch for severe ulcerative colitis were studied

Samples of proximal (20 cm from the ileocaecal valve· normal control) and distal (0–5 cm from the ileocaecal valve and ileostomy site) ileal mucosa and rectum were taken at pouch formation in nine patients for organ culture. Pouch mucosal biopsies were taken from ten patients before ileostomy closure and 3 months after closure in 14. Biopsies were taken from the posterior pouch corresponding to the site of the original proximal ileal sample.

Materials

Radioactive [^{3}H]glucosamine (740 GBq/mmol) and sodium [^{35}S]sulphate (2·04 GBq/mmol) were obtained from Amersham International (Amersham, UK) Cell culture products were purchased from Gibco, Edinburgh, UK, and Sepharose CL4B from Pharmacia/LKB, Milton Keynes, UK Other biochemicals were from Sigma Chemicals, Poole, UK.

Tissue samples

Mucosal biopsy samples were taken at surgery or pouch endoscopy, placed immediately on lens tissue soaked in complete medium, and maintained at room temperature during transfer to the laboratory before culture The maximum time between removal of tissue and initiation of culture was 60 min.

Organ culture

Organ culture was carried out as a modification of previous methods[10,11]. Four tissue squares were incubated per dish containing 2 ml Minimal Eagles medium with 10 per cent fetal calf serum, 100 units/ml penicillin, 100 μg/ml streptomycin and 150 μg/ml gentamicin. Radioactive precursors were added to the medium immediately before incubation (370 kBq [^{3}H]glucosamine, 925 kBq sodium [^{35}S]sulphate). The dishes were placed in Mackintosh jars, flushed with oxygen–carbon dioxide (95 per cent 5 per cent) for 5 min and incubated at 37°C for 24 h. After incubation, biopsies were washed with 1 ml phosphate-buffered saline (PBS) containing 1 mmol/l phenylmethylsulphonylfluoride, 5 mmol/l ethylenediamine tetra-acetic acid, 10 mmol/l benzamidine hydrochloride, 0·1 mg/ml soybean trypsin inhibitor and 10 mmol/l *N*-ethylmaleimide (protease inhibitors). Biopsies were homogenized in 1 ml PBS containing protease inhibitors, and a 200-μl aliquot taken for DNA determination Centrifugation for 5 min at 12 000*g* yielded the soluble cellular fraction and total membranes. The medium was removed from the dish and combined

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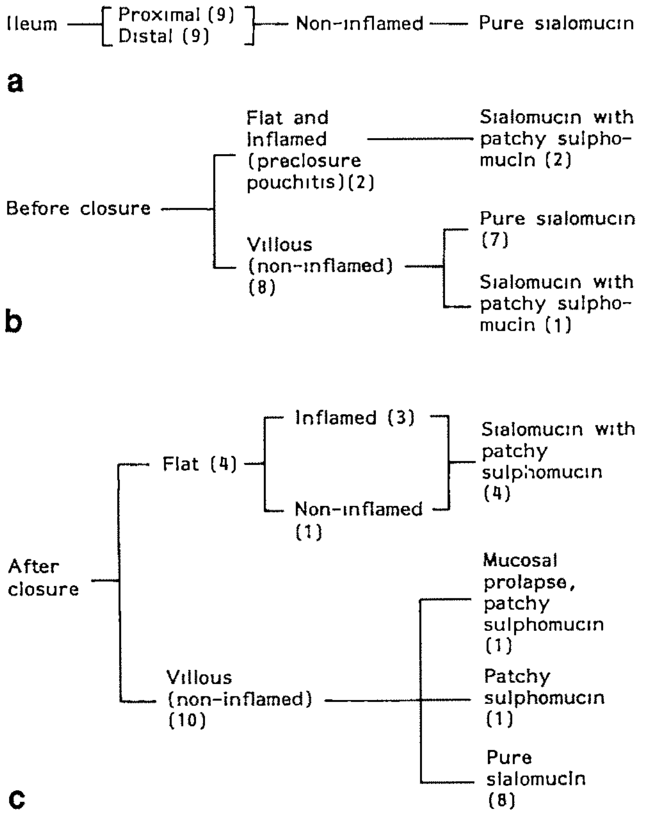
Ileum
Proximal (9)
Distal (9)
Non-inflamed
Pure sialomucin
a
Before closure
Flat and Inflamed (preclosure pouchitis) (2)
Sialomucin with patchy sulphomucin (2)
Villous (non-inflamed) (8)
Pure sialomucin (7)
Sialomucin with patchy sulphomucin (1)
b
After closure
Flat (4)
Inflamed (3)
Non-inflamed (1)
Sialomucin with patchy sulphomucin (4)
Villous (non-inflamed) (10)
Mucosal prolapse, patchy sulphomucin (1)
Patchy sulphomucin (1)
Pure sialomucin (8)
c

Figure 1 *Pouch mucin histochemistry. Tissue sections were stained by the high-iron–diamine method*[6] *Staining patterns are summarized for the tissue biopsies obtained at the different stages of pouch function* **a** *before pouch formation,* **b** *before ileostomy closure;* **c** *after ileostomy closure*

with the PBS washings before dialysis against three changes of distilled water (5 litres) at 4°C; this constituted the secreted fraction

Isolation of mucin fractions

Aliquots of the secreted (2 ml) and cellular (0·8 ml) fractions for all incubations were loaded on to columns (30 × 1 cm) of Sepharose CL4B equilibrated in 10 mmol/l Tris–HCl pH 8·0, and eluted with the same buffer, collecting 2-ml fractions The ^{35}S and ^{3}H content of each fraction was measured and the radioactivity in the high molecular weight peak eluting at the excluded volume (V_0) taken as the mucin component

Other methods

DNA was measured using a colorimetric assay[20]; radioactivity was determined as described previously[21]. Statistical analysis was carried out using the Mann–Whitney *U* test.

Histochemistry

The high-iron diamine–alcian blue method[6] was used with a fresh 40 per cent solution of ferric chloride at pH 1·4 and controlled with a standard composite block of ileum, stomach and right colon

Results

Clinical

Normal pouch function had been established in all patients at the time of biopsy (3 months after ileostomy closure). All were continent, with a median daily stool frequency of 4 (range 3–7).

Histochemistry

The results of histochemical staining are summarized in *Figure 1*. All proximal and distal ileal tissue was non-inflamed and stained for pure sialomucin. Pouch tissue both before and after closure was predominantly non-inflamed and characterized by pure sialomucin.

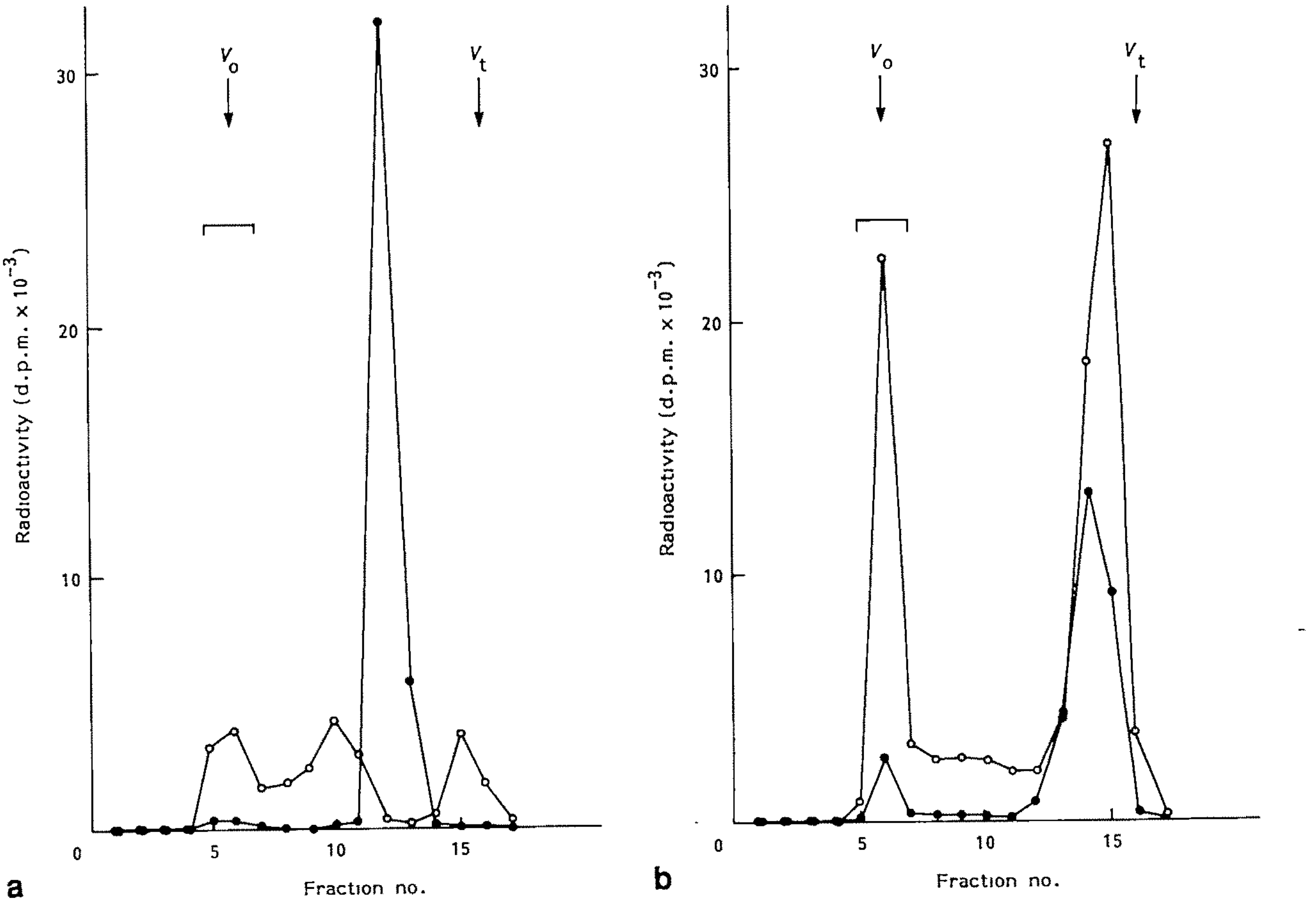

Figure 2 *Separation of mucin fractions by gel filtration. Elution profile of* **a** *secreted and* **b** *cellular fractions. Radioactivity as* ^{3}*H* (○) *and* ^{35}*S* (●). *The excluded* (V_0) *and total* (V_t) *volumes of the column are shown and the mucin fractions pooled as indicated*

Organ culture

The fractions obtained after organ culture gave typical profiles on Sepharose CL4B for the cellular and secreted material. The excluded (V_0) mucin fraction was well separated from all other components (*Figure 2*). The radiolabelled V_0 mucin fraction produced by mucosa from the ileum, rectum and pouch is shown in *Figures 3* and *4*. The ratio of ^{35}S:^{3}H incorporated (*Figure 3*) shows higher values for the mucins before and after closure in the cellular material than both ileal and rectal tissue, but this variation was significant only between tissue from the distal ileum and pouch after closure ($P < 0·006$). There was no difference in the ratios between the mucosa from 20 cm proximal to the ileostomy site or from the distal ileum or rectum.

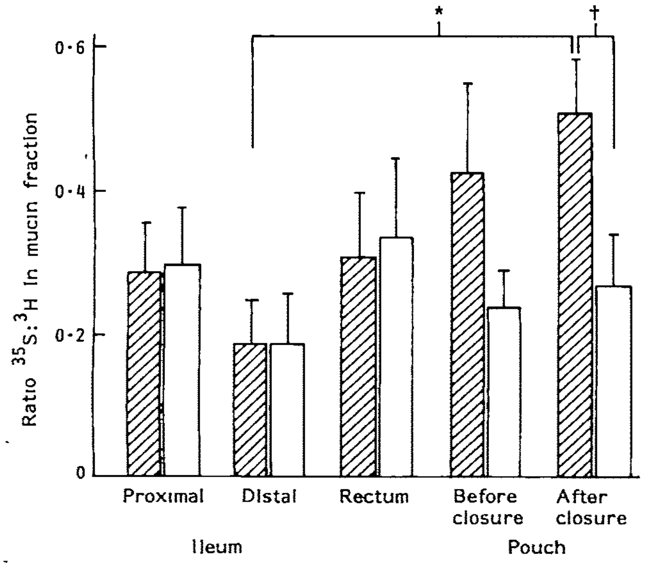

Figure 3 *Ratio of ^{35}S:^{3}H incorporation into cellular (■) and secreted (□) mucins. Values are mean(s.e.m.) ratio of total radioactivity in each mucin fraction (d.p.m. ^{35}S d.p.m. ^{3}H).* *P < 0·006, †P < 0·009 (*Mann–Whitney* U *test*)

Comparison of the ratios between the cellular and secreted mucins for individual tissue incubations showed significant variation in pouch tissue after closure ($P < 0·009$).

Variations in the amounts of [^{35}S]- and [^{3}H]-radiolabelled mucin synthesized were observed only in the secreted material (*Figure 4*). These variations were significant between proximal ileum and distal ileum, between proximal ileum and rectum, between proximal ileum and the pouch sample after closure, between rectum and the pouch sample before closure, and between pouch samples before and after closure.

No significant change was found in the amount of [^{35}S]- and [^{3}H]-radiolabelled cellular mucins in any of the tissues studied.

Discussion

The mucosal changes in mucin synthesis observed histochemically in patients with ulcerative colitis and after restorative proctocolectomy can be followed accurately using a dual-isotope metabolic labelling technique. The secreted mucin component can be measured, which is not possible using normal histochemical methods.

For the metabolic labelling technique to be valid, it is necessary for the mucins to be separated from the cultured fractions. Mucins can be separated from other glycoproteins using gel filtration[11] because of their characteristically high molecular weight (*Figure 2*). The results obtained show features typical of the histochemical changes caused by ulcerative colitis and as a result of restorative proctocolectomy relative to normal ileum and colon. The lack of difference in the ratio of labelling between the ileal and rectal samples suggests that the disease has led to a reduction in the level of sulphate in rectal mucins, rendering the patterns similar to those of normal ileum[1].

A difference in the turnover of [^{3}H]-radiolabelled secreted mucin in distal relative to proximal ileum indicates that the effects of colitis may extend beyond the colorectum or may

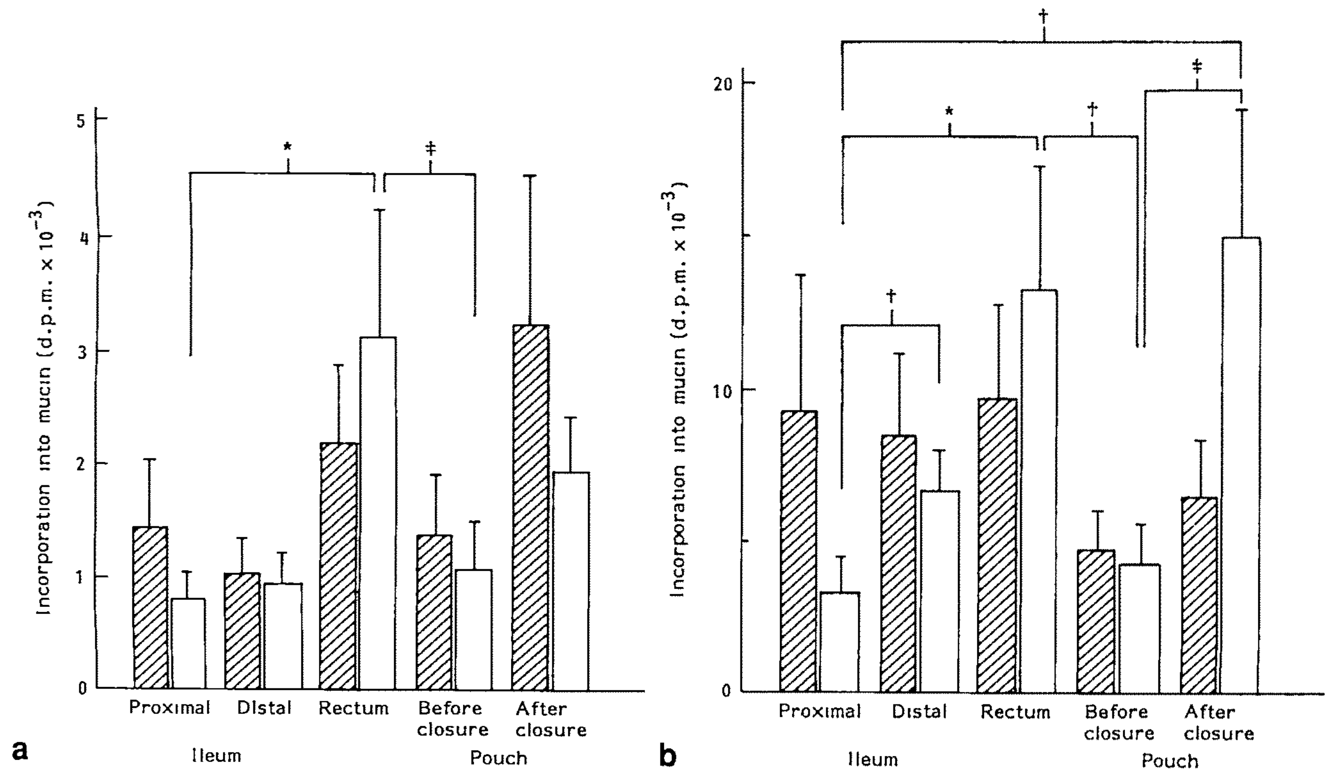

Figure 4 *Total incorporation of* **a** *^{35}S and* **b** *^{3}H into cellular (■) and secreted (□) mucins. Values are mean(s.e.m.) total radioactivity in each mucin fraction per µg DNA content of each incubation.* *P < 0·03, †P < 0·04, ‡P < 0·05 (*Mann–Whitney* U *test*)

change as a result of ileostomy, and underlines the importance of sampling at these two distinct ileal sites. Greater turnover of secreted mucin is seen in the rectum relative to the proximal (but not distal) ileum, further underlining the difference between the proximal and distal ileum. The general character of the mucin products in each tissue remains typical, so that ileum and colon can be easily discriminated[1]. These differences are clearly reflected in the labelled mucins isolated in this study.

Pouch biopsies taken before closure were characterized by a lower turnover of [^{3}H]-radiolabelled secreted mucins. This may reflect the response to defunctioning after pouch formation in the absence of a faecal stream[4]. Such pouches may occasionally become inflamed, probably as a result of defunctioning[22].

Pouch tissue taken after ileostomy closure showed the only significant change in the ratio of ^{35}S:^{3}H when compared with the distal ileum cellular mucins. In all samples after closure there was a difference between secreted and cellular mucin ratios. This suggests that an altered type of intracellular mucin is synthesized but that a normal mucin is secreted. It is probable that several different mucins exist and that changes in the regulation of their formation and secretion occur. Support for a change of mucosa after closure to rectal type is given by the observed increased synthesis of secreted mucin relative to proximal ileum and pouch material before closure.

Single-site biopsy sampling of the pouch in this study precludes any assessment of site-specific variation within the reservoir mucosa[2–5].

The mucin labelling technique confirms the histochemical data reported on ileoanal pouches[2–5] and is well suited for routine assessment of the function of the pouch mucosa.

The long-term functional behaviour of ileoanal reservoirs has not been evaluated. Careful monitoring is required to clarify mucosal changes with time and to assess any risk of neoplastic change[1–5].

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Evidence from dynamic integrated proctography to redefine anismus

The role of anismus in the aetiology of defective rectal evacuation was investigated by dynamic integrated proctography in 20 controls and 71 constipated patients. Normal parameters were defined and compared between 21 constipated patients with poor evacuation during proctography (<40 per cent of contrast evacuated; group 1) and 50 who evacuated fully (>90 per cent of contrast evacuated; group 2). Nine patients in group 1 failed to evacuate. Radiological abnormalities of the rectum were recorded in all groups but obstructed evacuation was not observed. Anismus (defined as a recruitment of puborectalis electromyogram (EMG) activity of >50 per cent) was significantly more common in group 1 than group 2 patients (14 of 21 versus *12 of 50,* $P < 0{\cdot}01$*) and present in seven of those unable to evacuate. Eight patients in group 1 failed to raise intrarectal pressure* $>50\ cmH_2O$ *compared with two in group 2* ($P < 0{\cdot}001$)*. Six patients in group 1 demonstrated both anismus and inability to raise intrarectal pressure, which may combine to cause defective evacuation. EMG recruitment alone is insufficient to diagnose anismus. Definition should be based on three criteria: demonstration of puborectalis EMG recruitment of* >50 *per cent; evidence of an adequate level of intrarectal pressure* ($>50\ cmH_2O$) *on straining; and presence of defective evacuation.*

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Evacuation of the rectum occurs by a complex and incompletely understood mechanism. Disorders of this mechanism may lead to defective evacuation quantitatively (inability to empty the rectum fully) and qualitatively where, even if emptying is complete, abnormal straining is required. Evacuation problems may arise from various causes including physical obstruction resulting from an anatomical abnormality of the rectum such as an intussusception[1], or a paradoxical contraction of the sphincteric mechanism during attempted evacuation. The latter condition, which is characterized by increased electromyogram (EMG) activity of the puborectalis muscle during straining, has been termed anismus[2].

The factors involved in evacuation have frequently been investigated in isolation, taking no account of possible relationships between them. To evacuate effectively, for example, there must be an adequate gradient of pressure from the rectum to the anus[2]. With adequate straining effort evacuation can occur despite sphincteric contraction. Reduced intrarectal pressure and inappropriate contraction of the pelvic floor musculature may therefore be inter-related in the pathogenesis of defective evacuation. Despite this, little account has been taken of intrarectal pressure in the investigation of anismus

Anismus occurs in normal subjects with no evacuation problems, leading to questions of its functional significance in constipated patients[3]. Confusion could, however, result from an indequate understanding. and definition of anismus in relation to abnormalities of evacuation.

The association and inter-relationship of puborectalis EMG activity and intrarectal pressure with differing types of evacuation were investigated in constipated patients and normal individuals using the technique of dynamic integrated proctography (DIP).

Patients and methods

DIP was carried out in 20 normal subjects (15 women, median age 47 (range 35–68) years) and 71 patients with constipation (62 women, median age 43 (range 19–77) years)

Dynamic integrated proctography

The DIP technique has been described in detail previously[4] EMG activity of the puborectalis was measured using fine-wire electrodes (7SS-2T; Clark Electromedical Instruments, Reading, UK) introduced percutaneously under local anaesthesia. The signal was integrated and amplified (Medelec MS6; Medelec, Woking, UK). Intrarectal pressure was initially monitored using a radiotelemetric capsule. This was superseded by a probe-mounted strain gauge of external diameter 2·1 mm (CTU-2; Gaeltec, Isle of Skye, UK) introduced peranally and connected to an amplifier (S7b, Gaeltec)

After lining the wall of the rectum with 30–40 ml barium sulphate suspension, a semisolid synthetic stool comprising barium sulphate, porridge oats and water (1:2 3) was introduced into the rectum until a constant desire to defaecate was reported (100–200 ml) With the patient seated on a water-filled portable commode (Porta Potti 165; Thetford UK, Thetford, UK) in relative seclusion, evacuation was screened laterally by radiography.

Using a customized software program, intrarectal pressure and EMG activity were displayed simultaneously with the screening on a radiograph monitor The procedure was recorded on videotape and EMG and intrarectal pressure data stored on floppy disc to enable hard copies to be made

The weight of contrast inserted into the rectum and voided was measured to estimate the percentage of contrast evacuated

EMG recruitment or inhibition was expressed as the percentage ratio of activity during evacuation divided by the basal activity at rest.

Two types of difficulty in evacuation were identified on DIP in constipated patients.

1 Group 1 were unable to evacuate >40 per cent of contrast despite straining for up to 5 min and were defined as having poor evacuation They had a quantitative and qualitative evacuation abnormality. This group included patients unable to evacuate during proctography.
2 Group 2 were able to evacuate >90 per cent of the contrast and were described as achieving full evacuation. Most of this group required a prolonged period of straining and therefore had a qualitative disorder of evacuation.

DIP parameters of EMG activity, intrarectal pressure and radiological abnormality were compared between these two patient groups and the normal subjects.

Radio-opaque marker transit studies were performed on all constipated patients. Fifty 1-mm barium-impregnated polyethylene pellets were ingested and an abdominal radiograph taken at 100 h

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Slow transit was defined as more than ten markers still *in situ* on the abdominal film

Statistical analysis

Differences between groups were analysed using χ^2 with Yates' correction

Results

Normal controls

DIP findings in the 20 normal controls are shown in *Table 1*. Puborectalis EMG activity during evacuation showed three patterns. The two most common were rapid inhibition with often only a small increase in intrarectal pressure needed to evacuate ($n = 8$), or an initial transient recruitment of EMG activity, which inhibited as straining continued ($n = 6$).

Four subjects demonstrated prolonged EMG recruitment despite complete evacuation. In these cases evacuation was achieved by abdominal straining to raise intrarectal pressure sufficiently to overcome anal resistance. Evacuation was completed within 1 min of straining irrespective of the pattern of evacuation.

As a result of these findings, anismus was defined as a recruitment of >50 per cent puborectalis EMG activity on straining with evidence of adequate straining effort witnessed by an intrarectal pressure >50 cmH_2O.

Constipated patients

Twenty-one patients were identified as group 1 (18 women, median age 37 (range 19–72) years). Of these, nine were unable to evacuate. Fifty patients evacuated fully (group 2: 44 women, median age 46 (range 19–77) years). The clinical symptoms of the constipated patients are shown in *Table 2*. These symptoms were absent in all control subjects. Only three of 50 patients in group 2 voided within 1 min of straining, confirming a qualitative abnormality of evacuation.

Radiological abnormalities of the rectum occurred with equal frequency in the two groups (*Table 3*), but in none was there evidence of physical obstruction to evacuation.

The incidence of EMG recruitment in the two groups is shown in *Table 4*. Anismus (EMG recruitment >50 per cent) was significantly more common in group 1 than group 2 and was particularly common in those unable to evacuate. A similar pattern was seen in the inability to achieve intrarectal pressure >50 cmH_2O (*Table 4*).

Table 1 *Findings in 20 control subjects during dynamic integrated proctography*

	No.	Median (range)
Electromyogram (%)		
Inhibition	14	−100 (−70 to 100)
No change	2	—
Recruitment	4	34 (7–70)
Intrarectal pressure (cmH_2O)	—	65 (50–140)
Evacuation (%)	—	87 (60–100)

Table 2 *Symptomatology in poorly evacuating and fully evacuating groups of constipated patients*

	Group 1 ($n = 21$)	Group 2 ($n = 50$)
Reduced stool frequency (<3 per week)	15	25
Prolonged straining at stool (>1 min)	16	34
Feeling of prolapse	13	13
Evacuation not complete	13	28

These symptoms were not found in the control subjects

Table 3 *Radiological abnormalities of the rectum detected by dynamic integrated proctography in patients and control subjects*

	Group 1 ($n = 21$)	Group 2 ($n = 50$)	Controls ($n = 20$)
Rectocele	9	14	3
Intussusception	2	14	1
Rectocele and intussusception	0	12	1

Table 4 *Incidence of anismus and reduced intrarectal pressure in group 1 and group 2 patients during evacuation*

	Group 1 ($n = 21$)	Unable to evacuate ($n = 9$)	Group 2 ($n = 50$)	*P**
EMG recruitment				
Present	16	7	14	
>50%	14	7	12	<0·01
Intrarectal pressure <50 cmH_2O	8	4	2	<0·001
EMG >50% and intrarectal pressure <50 cmH_2O	6	4	0	<0·001
Anismus by new criteria	8	3	9	

EMG, electromyogram. *Group 1 *versus* group 2 (Yates' χ^2 test)

A combination of these factors (i.e. EMG recruitment >50 per cent and reduced intrarectal pressure) occurred only in group 1. Of the six patients in whom both factors were found, only two evacuated contrast and in both this was <20 per cent. In these six patients (all women, median age 26 (range 23–45) years), four showed no abnormality of transit but two also had a diagnosis of slow-transit constipation from marker studies.

When anismus was redefined to take account of EMG recruitment >50 per cent, an adequate intrarectal pressure on straining (>50 cmH_2O) and evidence of defective evacuation (either quantitatively or in terms of prolonged straining), the incidence fell in both group 1 (from 14 to eight of 21) and group 2 (from 12 to nine of 50).

If anismus was defined solely as recruitment of EMG activity the problem was present in 30 patients and four control subjects.

Discussion

Anismus, based solely on EMG recruitment, has been described in patients with constipation during simulated defaecatory straining and evacuating simulated stool[2,4–8]. It could result from a failure, voluntary or involuntary, to relax the pelvic floor muscles[2], or an incoordination of these muscles analogous to urethral sphincter dyssynergia[5].

The functional importance of anismus in causing constipation has been questioned Bleijenberg and Kuijpers successfully treated seven of ten constipated patients with anismus by EMG biofeedback training to relax the pelvic floor muscles[9]. The success of other forms of therapy including myectomy[10,11] and botulinum toxin injection into the anal sphincter[12] has been limited. Jones *et al.* found EMG recruitment on attempted rectal balloon expulsion in 76 per cent of patients with constipation, and in 50 per cent of patients with solitary rectal ulcer and 48 per cent of those with perineal pain and normal expulsion[3]. In addition, EMG recruitment in constipated patients appeared inconstantly related to the ability to expel a rectal balloon[3] or to evacuate the rectum during DIP[8,13]

The present study has demonstrated EMG recruitment in normal individuals during DIP, despite an earlier report[4]. Failure to inhibit EMG activity while expelling rectal balloons has been noted in normal subjects[5].

Paradoxical puborectalis contraction during evacuation may result from the unfamiliarity and invasiveness of laboratory investigations[3] and may not be reproduced during evacuation in the patient's home environment[14].

The scepticism surrounding the diagnosis of anismus, arising from its detection in non-specific rectal conditions and normal subjects, and the limited success of treatment, could reflect inadequate diagnostic criteria based solely on EMG evidence. Three aspects appear to be important in adequately defining the condition: EMG recruitment, intrarectal pressure and defective evacuation.

Electromyogram recruitment

While EMG recruitment on attempted evacuation is not abnormal *per se*, the magnitude of recruitment may be. Only one control subject in this study recruited EMG activity >50 per cent (transiently reaching 70 per cent), whereas in patients with 'classical anismus' recruitment may reach many hundred times the basal level[8].

Intrarectal pressure

Some patients were unable to achieve the normal lower limit of intrarectal pressure on straining (50 cmH_2O). Intrarectal pressure reflects intra-abdominal pressure and, indirectly, the 'effort' of straining. Inadequate straining may result in a failure to evacuate; the causes of such straining are not clear but it could result from a conscious decision in some cases.

In combination, reduced intrarectal pressure and EMG recruitment both contribute to defective evacuation. In this situation anismus will be overdiagnosed unless account is taken of intrarectal pressure. The patients demonstrating this combination were a heterogenous group. Some had psychological problems, others responded to colectomy for synchronous slow colonic transit, implying that in these the findings of anismus were spurious. Normal evacuation following colectomy in similar patients has been previously described[9].

The DIP technique initially utilized a single manometer in the rectum. By placing a second transducer within the anal canal the expulsion pressure (anorectal pressure gradient) can be calculated A rise in intra-anal pressure during DIP gives corroborative evidence of paradoxical sphincteric contraction Evacuation depends on a positive anorectal pressure gradient, but in isolation this may not identify patients who do not strain adequately in the absence of puborectalis contraction. Two transducers are now used routinely during proctography.

Defective evacuation

It is important to exclude other causes of defective evacuation before attributing it to anismus. Radiological abnormalities during proctography are commonly found in normal subjects[15]. Intussusception is reported to cause obstructed defaecation[1] and large rectoceles causing difficulty in evacuation in some patients have been observed. In the present study no radiological abnormalities showed evidence of contributing to difficulty in evacuation.

Miller *et al.* suggested that for anismus to be considered functionally relevant it should be based on EMG findings and related to evidence of incomplete rectal evacuation[8]. Although many patients voided more or less fully, qualitatively the evacuation was not normal. Most required prolonged straining efforts of up to 3–4 min whereas normal subjects[16] fully evacuate the rectum in 30–60 s. Many complained of prolonged straining symptomatically. In the presence of adequate straining, anismus may contribute to an evacuation problem despite the ability to empty the rectum fully.

These suggested criteria should enable better selection of constipated patients with functionally significant anismus and improve their treatment.

Acknowledgements

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General surgery in patients aged 80 years and older

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This study reviews 594 surgical admissions, of patients aged 80 years and older, to departments of general surgery during 1 year. Half of the patients were admitted as emergencies and 60 per cent underwent surgery. The operative mortality rate was 8 per cent and the overall mortality rate for all admissions 9 per cent. The number of complications and the mortality rate after surgery increased in emergency cases and in patients with coexisting disease. Of all admissions, 72 per cent were uncomplicated and in 70 per cent patients could be discharged directly home; such patients do not generally take up beds and are discharged as soon as medical care is no longer indicated. The number of admissions of patients over 80 years of age will increase by about 30 per cent during this decade and, unless additional resources are provided to meet this challenge, new standards must be considered for the distribution of resources and of indications for surgery in both young and old.

In most Western countries the number of people over the age of 80 years is increasing, both in absolute terms and as a proportion of the total population. It may be expected that demands for surgical care of the elderly will rise during the next decade. Few data are available on the amount of surgical care needed by this population and this study was undertaken to provide information on the present surgical provision required for this age group

Patients and methods

All patients aged ≥80 years admitted to the departments of general surgery (including urology) in the county of Ringkobing, Denmark, between 1 April 1989 and 31 March 1990 were included prospectively in the study. Owing to local arrangements, patients with vascular surgical diseases are admitted to the departments of orthopaedics and are thus not included The population of the county is 267 000, of whom 8400 (3 per cent) are aged ≥80 years, 50 per cent of the total population are male, but in octogenarians and older only 38 per cent are male. There are five departments of general surgery: three in local hospitals and two in regional central hospitals.

Age, sex, and the dates of admission and discharge/death were recorded, in addition to the principal diagnosis on discharge, treatment while in hospital, complications and any significant concomitant disease. It was also recorded whether the patients were admitted as emergencies or in a planned fashion, and whether they were admitted from home or from another institution Destination on discharge was noted. The county statistical department provided population statistics and numerical estimates of the composition of the population at the end of the decade

Results

Patients admitted

During the study 434 patients were admitted on 594 occasions. A total of 85 patients were admitted twice, 20 three times, nine four times and two on more than four occasions. Women represented 41 per cent of patients, which means that 3 per cent of the total female population of this age group were admitted during 1 year compared with 8 per cent of men. If, however, sex-related diagnoses (prostatic and gynaecological disease, breast carcinoma) are excluded, the admission rate was 3 per cent for both sexes. The median age was 84 (range 80–99) years with no statistically significant difference between men and women. Emergencies comprised 50 per cent of admissions (*Table 1*), a little more than the emergency admissions of the departments as a whole Important coexisting disease was present in 51 per cent of patients, mostly ischaemic heart disease, chronic obstructive airway disease, or diabetes.

Length of hospital stay

The median stay was 8 (range 1–62) days. In the same period the median stay for patients as a whole was 5 days. All patients were discharged at the conclusion of surgical management except for 12 (2 per cent) whose stay was prolonged by 2–24 (median 8) days because of temporary lack of suitable accommodation after discharge.

Source of admissions

Almost 75 per cent of patients were admitted from home, where they managed on their own, some with varying degrees of support from family or social services. A group of 17 per cent were admitted from nursing homes or homes for the elderly and 9 per cent from other hospital departments. On discharge, nearly 70 per cent of patients were able to return home. The proportion of those discharged to a nursing home was about the same as that admitted from such a source (*Table 2*)

Cause of admissions

Malignant disease was the reason for admission in 31 per cent of cases (*Figures 1* and *2*). The majority of admissions in men were for urological, in particular prostatic, disease. Colorectal

Table 1 *Number of admissions*

	Men	Women	Total
Emergency	166	130	296
Planned	186	112	298
Total	352	242	594

Table 2 *Source of admissions and destination of discharges*

Source or destination	Admissions from source (%)	Discharges to destination (%)*
Home	74	70
Nursing home	17	16
Other hospital department	9	7

* A further 8 per cent died

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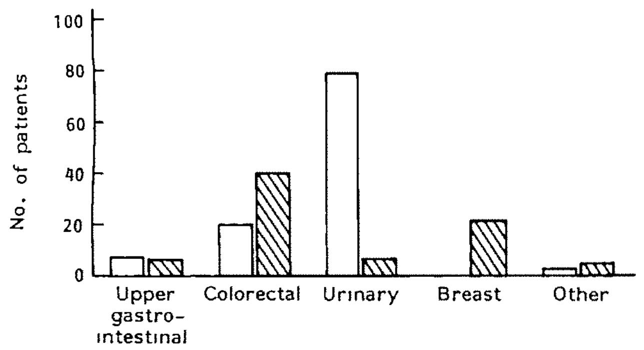

Figure 1 *Causes of 185 admissions with a malignant diagnosis.* □, *Men,* ■, *women*

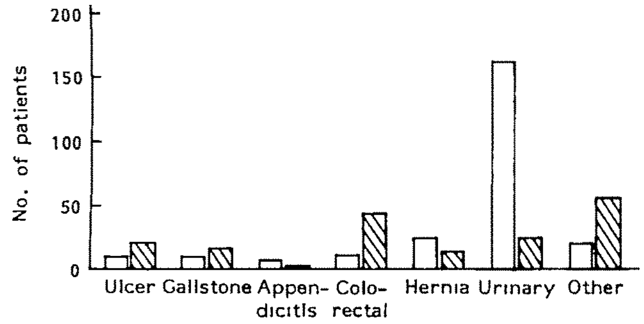

Figure 2 *Causes of 409 admissions with a benign diagnosis.* □, *Men;* ■, *women*

Table 3 *Operations performed*

Operation	Benign diagnosis	Malignant diagnosis	Total
Laparotomy			94
Ulcer	13	0	
Gallbladder disease	7	0	
Appendicitis	6	0	
Colorectal disease	8	40	
Other	17	3	
Herniotomy	31	0	31
Breast surgery	2	18	20
Transurethral surgery	94	34	128
Miscellaneous	59	26	85
Total	237	121	358

disease was the predominant diagnosis in women, 8 per cent of whom were admitted with carcinoma of the breast. Colorectal carcinoma was the cause of admission in 17 per cent of women but in only 6 per cent of men. However, excluding urological diagnoses, colorectal carcinoma accounted for 18 per cent of male admissions.

Operations

During their hospital stay, 358 patients (60 per cent of admissions) underwent surgery. Of patients with a benign diagnosis, 58 per cent had an operation, while 66 per cent with malignant disease underwent surgery. Of 298 patients admitted electively, 76 per cent were operated on, compared with 54 per cent admitted as emergencies. Details of the operations performed are shown in *Table 3*.

Complications

Of the 594 admissions, 72 per cent had no recorded complications. The remaining 165 patients had 214 complications (*Table 4*). Complications after operation occurred in 33 per cent of patients who underwent surgery, but 'complications' were also seen in patients for whom surgery was not indicated or contraindicated because of a 'complication' (*Table 4*). Twice as many complications were seen in patients with coexisting complicating disease as in those without concomitant morbidity. Also, the frequency of complications after operation was 45 per cent in emergency cases compared with 23 per cent in cases of planned surgery. The most common complication was myocardial infarction or cardiac arrhythmia, in patients undergoing operation, pneumonia and other infectious complications predominated. Wound infection was seen in 3 per cent of patients, all after emergency surgery.

Table 4 *Complications*

	Patients operated on	Patients not operated on	Total
Heart failure	40	15	55
Apoplectic stroke	2	0	2
Thromboembolism	2	0	2
Infection			
Pneumonia	26	4	30
Septicaemia	2	4	6
Urinary	39	8	47
Wound	9	0	9
Other	3	1	4
Other	38	21	59
Total	161	53	214

Table 5 *Causes of death*

	Patients operated on	Patients not operated on	Total
Heart failure	19	7	26
Pneumonia	3	0	3
Renal failure	2	4	6
Pulmonary embolism	2	0	2
Apoplectic stroke	2	0	2
Gastrointestinal haemorrhage	0	4	4
Septicaemia	0	3	3
Cachexia	1	4	5
Total	29	22	51

Mortality

The overall mortality rate was 9 per cent (51 patients). The mortality rate ranged from zero of 107 patients with no complicating disease undergoing elective surgery to 20 of 97 emergency cases (21 per cent) with important concomitant disease. There were 63 emergency operations in patients without complicating disease and the mortality rate was 6 per cent. Heart failure was by far the most common cause of death (*Table 5*). Thromboembolic complications caused death in two patients (0·5 per cent). Of those who died, 49 per cent had a diagnosis of malignancy, compared with 31 per cent of all patients admitted.

Discussion

Surgery in the elderly carries a risk, but it should not be characterized by defeatism. The majority of patients are admitted for benign conditions and elective surgery can be carried out with an acceptable number of complications and a low mortality rate; 72 per cent of all admissions had no complications. It appears that morbidity and mortality after operation do not depend so much on age *per se*, but are related to the coincidental medical problems present before surgery. This has also been found in other studies[1–3]. In addition, emergency surgery further increases the risk of complications and death. It has been suggested that early surgical treatment is often advisable in the elderly[2,4], as the risk of turning an elective operation into an emergency one, thereby adding to the probability of complications, is increased by delay. Efforts should be made to adjust and correct any concomitant disease before surgery, although this may be difficult in urgent cases. The complication and mortality rates in this study compare favourably with those of other studies[2,5–8]. Half of the patients who died had malignant disease, and 20 per cent of these died not from complications but from cachexia.

It is often assumed that elderly patients who no longer need inpatient medical or nursing care frequently take up beds longer than younger individuals. In other studies this has not been found to be the case[6,8,9] and the present study confirms this. Few patients stayed longer than medically indicated and, despite 70 per cent being discharged home, the median hospital stay was only 8 days The median stay for patients admitted to the surgical departments as a whole was 5 days; in general the prolonged hospitalization of the elderly results from morbidity after surgery and is not related to social factors.

The incidence of malignant disease increases dramatically with age[10] and one-third of admitted patients had cancer. Colorectal carcinoma in this age group has been reported to be slightly commoner in women than in men[10] and this was confirmed in the present study. Most of the higher admission rate for men was for prostatic disease but, even if specific sex-related diagnoses are excluded, the admission rate in relation to the number and composition of octogenarians and older in the population was almost twice as high for men as for women. This means that men had multiple admissions more often than women. There is no obvious explanation for this difference.

Estimates of the composition of the population of Ringkobing county suggest a 24 per cent increase in octogenarians and older during this decade, from 8400 in 1990 to 10400 in 2001. With an unchanged sex ratio and unaltered admission rates, there will be a corresponding rise in hospital admissions of patients over 80 years. This increase will certainly be noticeable, as estimates of the population under 80 years suggest little change. Furthermore, orthopaedic and vascular surgery were not included in the present study and the demands on these specialties are increasing, perhaps especially with respect to the elderly. A recent study in the UK[8] demonstrated the same tendency and the results are probably applicable to most countries of the Western world, both to those in which all hospitals are tax-financed non-payment public institutions (as in Denmark) and to those in which hospitals are subject to varying degrees of private enterprise

To meet this future challenge one or more of the following demands must be met:

1. More resources must be made available.
2. Priority concerning certain groups of patients, certain diagnoses, or certain treatments must be decided.
3. More surgery must be performed on an outpatient basis. This may be difficult in elderly patients, half of whom are admitted as emergencies and more than half of whom have concomitant medical problems.
4. New treatments with lower morbidity rates, earlier recovery and reduced hospital stay must be developed. Laparoscopic and endoscopic surgery seem promising in this respect and may be particularly valuable in the treatment of the elderly.

Further research in surgical methods, indications for and organization of surgery is warranted, and a comprehensive professional and political discussion concerning priority and distribution of resources is urgently needed.

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Surgical Research Society Abstracts

Br. J. Surg. 1992, Vol. 79, November, 1219–1243

The following abstracts were presented at the 76th meeting of the Surgical Research Society, with Professor L. E. Hughes in the chair. The meeting was held on 2–3 July 1992 at the University of Edinburgh and was organized by the University Department of Surgery. One hundred and nine papers were presented during the scientific sessions, which were preceded by a symposium entitled 'Molecular genetics in cancer'. The Patey Prize was awarded to Mr C. H. Wakefield of St Mary's Hospital, London, for his paper entitled 'Surgical significance of neutrophil phosphatidylinositol glycan-tailed receptors'.

Influence of total colectomy on serum antineutrophil cytoplasmic antibodies in inflammatory bowel disease

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Perinuclear antineutrophil cytoplasmic antibodies (pANCAs) have previously been demonstrated in patients with various forms of vasculitis and more recently in inflammatory bowel disease by an indirect immunofluorescence technique

The serum of 90 patients was tested for pANCA. Of these patients, 55 had ulcerative colitis (UC) 19 with varying grades of UC, 13 after subtotal colectomy for UC and 23 after restorative proctocolectomy (RPC) for UC. A further 18 had Crohn's disease, five indeterminate colitis and 12 without inflammatory bowel disease acted as controls

Overall the prevalence of pANCAs in UC was 75 per cent (41 of 55) but pANCAs were still present in the RPC group (74 per cent: 17 of 23), where the mean follow-up was 1·3 years. All four patients who had pouchitis following RPC were positive for pANCA In contrast, 28 per cent (five of 18) of patients with Crohn's disease had pANCA, four of the five had Crohn's colitis and three had undergone subtotal colectomy. pANCAs were not detected in controls

These results show that pANCAs are more prevalent in colonic inflammatory bowel disease, especially UC. The persistence of pANCAs in the sera over 1 year after RPC suggests that the antigen or antigens are not fully eradicated and therefore it is not just the colon that is targeted immunologically in UC.

Effect of L-arginine on lymphocyte transformation in patients with breast cancer

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The amino acid L-arginine increases lymphocyte blastogenesis in response to mitogens in healthy volunteers and reduces postoperative immune suppression The effect of arginine on general lymphocyte reactivity in patients with untreated malignancy has not been described previously. Immunosuppression is well documented in patients with cancer and relates to tumour burden.

This study assessed the effect of oral arginine supplementation (30 g day^{-1} for 3 days) on T and B lymphocyte mitogenic reactivity in 12 patients with locally advanced breast cancer The responses to phytohaemagglutinin (PHA), conconavalin A (Con A) and pokeweed (PWM) mitogens are expressed as stimulation indices (SI), where SI is mean maximum c p m./unstimulated culture c.p.m

	Before arginine	After arginine	*P**
Con A	22(5)	43(16)	<0·001
PHA	84(13)	133(26)	<0·001
PWM	24(5)	38(10)	0·011

Values are mean(s.e.m.) * Paired *t* test on log transformed data

Arginine did not produce any change in total lymphocyte counts, CD4/CD8 subsets or the expression of the interleukin 2 (IL-2) receptor CD25, as measured by FACS analysis Measurement of cytokine levels in patients' serum (enzyme-linked immunosorbent assays) showed no changes in interleukin 1 beta, IL-2, interferon gamma and tumour necrosis factor alpha These are the first documented results revealing a stimulatory effect of L-arginine on general lymphocyte reactivity in patients with cancer Arginine may have a role in increasing host defences in the immunocompromised patient with cancer before and during the perioperative period

Effect of adjunctive intraoperative photodynamic therapy on local recurrence of colorectal cancer in a murine model

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It is postulated that adjunctive intraoperative photodynamic therapy (AIOPDT) may reduce local recurrence of colorectal cancer. Photofrin, a photosensitizing agent that is selectively retained in tumour, is injected 24–48 h before surgery. After tumour excision, the tumour bed is irradiated with laser light to destroy any residual neoplasm.

This study investigated the efficacy of AIOPDT using COLO26 tumour local recurrence in BALB/c mice as a model, and evaluated the impact of light wavelength and dose on outcome. Tumours were grown subcutaneously in the left hind leg. A standardized surgical resection was performed to remove all visible tumour Study groups 1–4 received 15 mg kg^{-1} photofrin 24 h before surgery. Tumour beds were irradiated with 630-nm light at 40 and 70 J cm^{-2} (groups 1 and 2 respectively) or 510-nm laser light at 40 and 70 J cm^{-2} (groups 3 and 4 respectively). Control groups 5–8 received either surgery only (group 5), surgery and photofrin only (group 6) or surgery and either 630-nm (group 7) or 510-nm (group 8) light

Group no.	No. of mice	Mean(s.d.) tumour weight (g)	Recurrence*
1	18	0·56(0·11)	6 (33)†
2	17	0·56(0·08)	3 (18)†
3	18	0·56(0·08)	5 (28)†
4	18	0·59(0·11)	3 (17)†
5	31	0·53(0·15)	27 (87)
6	11	0·57(0·14)	11 (100)‡
7	12	0·54(0·13)	10 (83)‡
8	12	0·55(0·14)	10 (83)‡

* Values in parentheses are percentages † $P < 0{\cdot}05$ *versus* groups 5–8, ‡ *P* not significant *versus* group 5 (χ^2 test)

AIOPDT using the above light parameters reduced local recurrence of excised COLO26 tumours Light dose but not light wavelength affected the outcome

Beneficial effects of defocused carbon dioxide laser irradiation in experimental peptic ulceration

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The defocused CO_2 laser selectively destroys vagal nerve fibres while preserving blood vessels. This study assessed a novel approach for the

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treatment of experimental peptic ulceration using this laser to irradiate the stomach. Sixty male Sprague–Dawley rats (300–400 g) were anaesthetized and randomized to four groups. group 1 underwent sham laparotomy (control), group 2 surgical highly selective vagotomy (HSV); group 3 defocused serosal irradiation with the CO_2 laser (laser-S), and group 4 defocused mucosal irradiation with the laser via a gastrotomy (laser-M) Laser irradiation was performed at 5-W setting and a focal diameter of 10 mm was used After 2 weeks' recovery, cysteamine (400 mg kg^{-1}) was injected subcutaneously to induce peptic ulceration. Stomachs were examined blindly at 24 h for pH, number of ulcers and ulcer index ($\leqslant 0{\cdot}2$ cm, 0·5; $>0{\cdot}2$ cm, 1·0 per animal).

Group	*n*	Mean ulcers per animal	Ulcer index	pH
Control	15	6·5	4·3	1·4
HSV	15	2·7*	1·7*	4·2*
Laser-S	15	1·2*	0·9*	4·3*
Laser-M	15	2·1*	1·7*	3·0*

* $P<0{\cdot}05$ *versus* control (Student's *t* test)

Defocused CO_2 laser treatment of either serosal or mucosal surfaces significantly reduced acid production and was as successful as HSV in preventing ulceration This new technique could be administered by laparoscopy to the serosal surface or by gastroscopy to the gastric mucosa, and offers an interesting approach to the endoscopic management of peptic ulcer disease

Control of neutrophil and endothelial responses by leukotrienes during postischaemic reperfusion

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During postischaemic reperfusion, free radicals promote lipid peroxidation of endothelial and particularly neutrophil cell membranes, releasing peptidoleukotrienes C_4, D_4, E_4 (PLTs) (vasoconstriction, vasopermeability) and B_4 (LTB_4) (neutrophil chemotaxis, activation). This study assessed PTL influence on indices (reperfused · contralateral normal limb) of muscle viability (nitroblue tetrazolium) and oedema (wet weight.dry weight) in rats. The rats underwent 6-h unilateral hindlimb ischaemia and 4-h reperfusion after intravenous infusion of specific receptor antagonists (RA) to PLT (ICI 198615, 550 μg per kg per 4·5 h) or LTB_4 (SC 41930; 1 mg per kg per 4·5 h) starting 30 min before revascularization. Results were compared with normal and control (no infusion) rats

Group	*n*	Viability index*	Oedema index*
Normal	10	1·00 (1·00–1·00)	1·00 (0·98–1·01)
Control	12	0·53 (0·33–0·61)	1·23 (1·09–1·37)
PLT RA	8	0·29 (0·17–0·33)	1·26 (1·20–1·31)
LTB_4 RA	12	1·00 (1·00–1·00)	1·08 (1·05–1·10)

* Values are mean (range)

Muscle infarction and oedema during reperfusion (control *versus* normal, $P<0{\cdot}01$) were prevented by the LTB_4 RA (*P* not significant *versus* normal; $P<0{\cdot}01$ *versus* control) but not by the PLT RA ($P<0{\cdot}01$ *versus* normal, LTB_4 RA), which exacerbated muscle necrosis ($P<0{\cdot}05$ *versus* control) Thus in skeletal muscle LTB_4-mediated neutrophil activation promotes reperfusion injury while PLT appears beneficial in the microcirculation, possibly as a result of PLT-mediated release of prostacyclin and endothelium-derived relaxing factor.

Prediction of complications after gastric cancer surgery in a Japanese population

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Japanese surgeons report exceptionally low morbidity rates after extended radical gastrectomy for cancer compared with Western authors To investigate the reasons for this, a retrospective study was performed of preoperative and perioperative factors that might influence the risk of complications in Japanese patients

A group of 204 patients who experienced complications resulting in delayed discharge or death following gastrectomy for cancer were matched for age, operation type and year of operation with 187 patients whose postoperative course was uneventful. Risk factors studied were. age, obesity, index, tumour stage, creatinine, albumin, serum glutamic–oxaloacetic transaminase, lymphocyte count, forced expiratory volume per second/forced vital capacity, systolic blood pressure, electrocardiogram (ECG) abnormalities, operating time and operative blood loss A multivariate analysis using multiple logistic regression allowed calculation of the significance of each factor as a change in deviance (CD) value.

Only operative blood loss (CD 21), ECG abnormality (CD 5·08), systolic blood pressure > 140 mmHg (CD 4·64) and obesity (CD 7·48) had independent predictive value. Age increases the severity but not the frequency of complications (CD 10)

Operative blood loss is the best predictor of complications after operation in this population. Japanese patients suffering from obesity, heart disease or hypertension are at increased risk of complications These factors may have relevance to the comparison of complication rates in Western and Japanese patients

Non-absorption of luminal contents by obstructed small intestine

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A change from net absorption to net secretion occurs in small bowel obstruction. Previous studies have shown that small bowel absorption depends on luminal oxygen and energy substrates This study investigated the effect of small bowel obstruction on luminal partial pressure of oxygen (P_{O_2}). Twenty male Sprague–Dawley rats were anaesthetized with subcutaneous pentobarbitone and distal ileum cannulated with a P_{O_2} probe. In ten of the rats a ligature distal to the probe was tied (causing obstruction) at time zero and released at 90 min. Intraluminal pressure was measured using a pressure transducer.

Time (min)	Mean(s.d.) P_{O_2} (kPa) Control	Obstruction	*P**
−1	3·86(0·42)	3·77(0·14)	0·54
0	3·85(0·36)	3·77(0·13)	0·59
10	3·84(0·38)	3·31(0·42)	0·02
20	3·63(0·73)	2·85(0·70)	0·05
30	3·89(0·42)	2·67(0·51)	0·0001
60	3·93(0·42)	1·91(0·77)	0·0001
90	3·89(0·41)	1·57(0·94)	0·0001
100	3·49(0·28)	1·98(0·89)	0·01
120	3·43(0·34)	3·32(0·25)	0·73

Intraluminal pressure did not exceed 5 cmH_2O * Student's unpaired *t* test

Luminal P_{O_2} fell significantly with small bowel obstruction and rose when obstruction was relieved No significant pressure change occurred. Absorption (requiring active transport using aerobically metabolized energy substrates) stops because of a fall in luminal P_{O_2} that occurs in obstruction Small intestine cannot obtain enough oxygen for absorption from the local gut circulation directly

Identification of a new transiently activated early-response gene in colonic epithelial cells

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Sodium butyrate, a product of fibre fermentation in the colon, has been shown to modulate levels of growth factors and their receptors, suggesting a direct link between diet and regulation of cell proliferation Direct demonstration of this, however, has been problematic Cell proliferation is controlled by growth factors inducing nuclear factors that regulate transcription. Southern and Northern blotting have identified a new human gene, hcMG1, which may specify such a nuclear protein.

hcMG1 is very similar to cMG1, a rat intestinal gene that is transiently activated in response to epidermal growth factor (EGF) and believed to specify a nuclear factor hcMG1 shows sequence similarity to a murine, mitogen-inducible nuclear protein, TIS11, at a site believed to involve DNA binding.

Further Northern blot analysis has indicated that the human homologue is EGF-inducible. hcMG1 has been cloned via a novel messenger RNA enrichment technique using biotinylated antisense DNA and streptavidin-coated magnetic beads. DNA sequence analysis shows that hcMG1, cMG1 and TIS11 have no similarity with known early-response genes and may therefore belong to a new family of mitogen-induced genes specifying nuclear factors. Understanding its regulation may identify the link between effects of nutritional factors and genetic control of gastrointestinal cell proliferation

Tumour levels of pS2, cathepsin D and steroid receptors in women with early breast cancer

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Tumour levels of the oestrogen-regulated proteins pS2 and cathepsin D (Cat-D) may provide additional prognostic information to that given by steroid receptors.

In this study oestrogen (ER) and progesterone (PR) receptor protein levels (enzyme immunoassays) were compared with pS2 and Cat-D protein levels (radioimmunoassays) in tumours from 83 patients entered into a prospective randomized trial of lumpectomy with or without radiotherapy with adjuvant tamoxifen for 2 years or to relapse. Cut-off values for positive status were $\geqslant 20\,\mathrm{fmol\,mg^{-1}}$ for ER and PR, $\geqslant 1{\cdot}0\,\mathrm{ng\,mg^{-1}}$ for pS2 and $\geqslant 35\,\mathrm{pmol\,mg^{-1}}$ for Cat-D.

ER and PR were significantly correlated with each other (Kendall's $\tau = 0{\cdot}364$, $P < 0{\cdot}00001$) and with pS2 ($\tau = 0{\cdot}261$, $P < 0{\cdot}0005$ and $\tau = 0{\cdot}27$, $P < 0{\cdot}0005$, respectively), but none of these proteins correlated with Cat-D. Histologically small tumours ($\leqslant 2$ cm) tended to have higher ER ($\chi^2 = 7{\cdot}9$, $P = 0{\cdot}005$), PR ($\chi^2 = 10{\cdot}8$, $P = 0{\cdot}001$) and pS2 ($\chi^2 = 8{\cdot}7$, $P = 0{\cdot}003$) but similar Cat-D levels compared with larger tumours ($>$2–5 cm). Histological grade ($n = 59$) correlated (χ^2 for linear trend) with protein marker status for ER ($\chi^2 = 18{\cdot}6$, $P < 0{\cdot}0001$), PR ($\chi^2 = 10{\cdot}8$, $P = 0{\cdot}001$) and pS2 ($\chi^2 = 5{\cdot}8$, $P = 0{\cdot}016$) but not Cat-D ($\chi^2 = 3{\cdot}0$, $P = 0{\cdot}08$).

To date, with a median follow-up of 16 months, there have been 11 recurrences and four deaths in this subset of trial patients Of these, eight (three deaths) were ER negative ($n = 23$), nine (four) were PR negative ($n = 36$), nine (four) were pS2 negative ($n = 41$) and six (three) were Cat-D negative ($n = 43$). Ten of the recurrences and the four deaths occurred in patients with tumours negative for at least two of three proteins, i.e ER, PR, pS2 ($n = 27$) or ER, PR, Cat-D ($n = 30$).

Tumour pS2 and Cat-D, in combination with ER and PR, may be useful prognostic markers in women undergoing lumpectomy for node-negative early breast cancer

Flow and static cytometry in the automated analysis of grading in breast cancer

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Histological grade is a strong independent predictor of prognosis in breast cancer but has not gained widespread acceptance because of poor intercentre reproducibility. An objective measurement using machine technology could give better reproducibility This study describes a score derived from quantitative flow and static cytometry.

The morphometric variable standard deviation of nuclear size (OBSZSD) replaced nuclear pleomorphism and was measured by image analysis (CAS 200) Proliferative index (PI) replaced mitotic rate and was measured by flow cytometry. Oestrogen receptor status, c-*erb*B2 and NCRC-11 staining were assessed as surrogate measures of tubule formation/functional differentiation. In a stepwise multiple regression analysis controlling for grade, only OBSZSD and PI showed independent association. By combining these two variables a 'grade equivalent' (Score) was derived·

$$\text{Score} = \text{OBSZSD} + \text{PI}$$

	Histological grade		
Score	1	2	3
1	28	22	16
2	25	77	25
3	7	34	97

$\chi^2 = 92{\cdot}3$, 4 d f, $P < 0{\cdot}0001$

In discriminant analysis for grade, the Score predicts 72 per cent of cases correctly.

This is an objective measure of histological grade using flow and static cytometry and can be calculated by technical officers Because the Score predicts the histological grade correctly in over 70 per cent of cases, this reproducible cytological grading system should be of value in clinical practice

Uptake of dehydroepiandrosterone sulphate into breast cyst fluid

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The androgen conjugate dehydroepiandrosterone sulphate (DHAS) is found in high concentrations (average 100 times concentration in plasma) in human breast cyst fluids. The amount present correlates with electrolyte composition· type I cyst fluids have a low $\mathrm{Na^+\,K^+}$ ratio and high concentrations of DHAS and type II fluids have a high $\mathrm{Na^+{:}K^+}$ ratio and lower levels of DHAS This study investigated the uptake of DHAS into cyst fluids.

A volume of 1 MBq [^{3}H]DHAS was continuously infused intravenously in ten patients with multiple cysts· 165 (124 type I, 41 type II) cysts were aspirated over 4 h (one patient), 24–28 h (five patients) or 48–52 h (four patients) By 28 h levels of radioactivity were substantially higher in cyst fluids than in plasma from three patients and by 52 h levels were up to six times higher than in plasma Of the 41 cysts that had higher levels of [^{3}H]DHAS than plasma, all 41 were type I Cysts aspirated at 3 weeks (four patients), 3 months (one cyst) and 5 months (one cyst) showed persisting levels of radioactivity in the absence of detectable radioactivity in plasma.

[^{3}H]DHAS is taken up into breast cyst fluids against a concentration gradient over a number of days and remains there for months. Uptake above plasma levels occurs only in type I cysts

Preoperative diagnosis in breast cancer

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A major benefit of the national breast screening programme has been increased expertise in breast radiology and cytology, which now allows preoperative diagnosis of most breast cancers In this study 156 women with screen-detected invasive breast cancers were analysed for mode and timing of diagnosis Preoperative diagnosis was achieved in 112 (72 per cent).

Of the 58 women who had clinically apparent tumours all but one, a lobular carcinoma, were diagnosed before operation (54 by fine-needle aspiration cytology (FNAC), three by core biopsy). Forty women had vaguely palpable lesions with ultrasonographic assistance (radiologically palpable), of whom 36 were diagnosed before operation (all FNAC). A further 33 women had impalpable cancers, but these could be visualized on ultrasonography, allowing preoperative diagnosis in 17 cases (all FNAC). The remaining 25 patients in the total cohort had impalpable, ultrasonographically negative tumours and only two were diagnosed before operation Increased experience with stereotactically guided cytology should improve the diagnostic rate in this group.

Ultrasonographic assessment simultaneous with clinical examination is recommended as it allows diagnostic confirmation of many small tumours, facilitating patient counselling, operative planning and a reduction in the total number of operations required.

Avoidance of dissection of the axilla in screen-detected breast cancer

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The management of axillary nodes in screen-detected breast cancer is controversial Optimal treatment should combine accurate node status with the avoidance of unnecessary morbidity.

The aim of this study was to determine whether full axillary dissection can be avoided in some women with screen-detected breast cancer. Since October 1988, 223 breast cancers were found via our screening programme A total of 180 were invasive, of which 40 were found to be lymph node positive. The presence of involved nodes was associated with large tumour size ($P \leqslant 0{\cdot}0001$), high tumour grade ($P \leqslant 0{\cdot}0001$) and the absence of mammographic microcalcification ($P \leqslant 0{\cdot}05$) (statistics by Yates' χ^2)

Pathological tumour size (cm)	Grade of tumour			No of involved axillae by grade		
	1	2	3	1	2	3
<1	16	12	3	0	0	1
1–1·9	25	43	9	1	10	5
2–2·9	4	19	7	0	7	5
⩾3	4	12	6	2	5	4

These observations differ from those of other authors in finding that node negativity is associated with microcalcification

In conclusion, women with screen-detected breast cancer <1 cm in size or those with grade 1 tumours of <3 cm could avoid extensive axillary surgery and thus obtain reduction in operating time and morbidity

Psychosocial measurements in Poland's syndrome

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Thirty-two consecutive patients with Poland's syndrome presenting over an 8-year period were reviewed Psychometric evaluation of satisfaction, body image perception, and physical and social functioning was made. The mean age of the patients was 24·8 (range 15–33) years Prevalence of adverse social and physical antenatal influence was evident. Twenty-eight patients underwent surgical reconstruction of the breast. 19 augmentation mammoplasty (four chose to have both sides augmented), six reduction mammoplasty and three required both procedures to achieve symmetry One patient declined surgery and three were put on low-dose tamoxifen.

The reasons for wanting surgery were inability to take part in physical, social and sexual activities; disparagement, and lowered self-esteem Some 76 per cent of patients perceived a loss of femininity and experienced a feeling of inadequacy, and 92 per cent expressed anxiety regarding marriage, sex and relationships.

Results of patient satisfaction (scars, shape, size and symmetry) showed 70 per cent of patients felt overall satisfaction with the surgery. In all, 16 per cent of the patients required revisional surgery In the silhouette (draw-a-woman) test, 12 of 17 women showed size after surgery and ideal size to be similar. Body image perceptions measured by the body attitude questionnaire had subscales comprising disparagement, salience and feeling of attractiveness Patients with Poland's syndrome had a significantly raised feeling of disparagement (mean(s.d) 23 8(5·9)) and lowered self-esteem (mean(s d.) 10 8(3 4)) compared with a normal population ($P < 0{\cdot}025$).

Generation of lipid peroxides in the de-endothelialized rabbit aorta

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Peroxidation of lipids increases their atherogenicity This process has been implicated in both the initiation of atherosclerosis and restenosis following angioplasty. The relationship between intimal injury and lipid peroxide (LPO) production in a rabbit model was investigated

Male New Zealand White rabbits underwent de-endothelialization with a 3-Fr Fogarty catheter At 2 weeks the rabbits were killed and the aortas harvested Sections of size 1 cm^2 were analysed fluorometrically for LPO content and compared with normal aorta De-endothelialization produced a tenfold increase in LPO levels To assess the effect of thrombin inhibition, the thrombin antagonists D-phenylalanyl-L-arginine chloromethylketone (PPACK) and recombinant hirudin were administered. PPACK (2·5 mg per 100 μl) was delivered over 7 days by an osmotic minipump implanted at the time of de-endothelialization, hirudin (1 mg kg^{-1}) was given intravenously immediately before balloon de-endothelialization

	n	Lipid hydroperoxide (nmol H_2O_2 per g tissue)
Control	8	0·98 (0·38–1·57)*†
De-endothelialization	8	21·65 (16·78–25·72)‡
Thrombin inhibition with de-endothelialization	8	1·63 (0·80–2·05)

Values are median (interquartile range) $^*P = 0{\cdot}03$ *versus* de-endothelialization (97 per cent confidence interval of difference 13·73–26·55), $^\dagger P = 0{\cdot}31$ *versus* thrombin inhibition with de-endothelialization, $^\ddagger P = 0{\cdot}03$ *versus* thrombin inhibition with de-endothelialization (97 per cent confidence interval of difference 11·01–25·12) (Mann–Whitney *U* test)

LPO is known to be associated with the development of intimal hyperplasia and this study shows high levels following intimal trauma to the rabbit aorta Suppression of LPO by thrombin antagonists may have important implications for improving the outcome of surgery for peripheral vascular disease

Urokinase production in organizing thrombus

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Urokinase plasminogen activator (uPA) is prominent in granulation tissue and tumours but found in only low concentrations in normal blood vessels Tissue plasminogen activator (tPA) was considered to be the agent of vascular thrombolysis because of its high vascular concentration and fibrin specificity. The histological appearance of organizing thrombus suggests a role for uPA In this study thrombi were raised in rat inferior vena cava (IVC) using thrombin and flow reduction. The thrombi and surrounding IVC were removed from groups of ten thrombosed rats and ten control rats at eight intervals from 1 h to 21 days. Specific bioimmunoassays measured the tPA and uPA contents of the homogenized tissue samples

	Normal	1 h	2 days	7 days	14 days
Thrombus tPA	—	2·6(0·6)	2·3(0·9)	4·5(3·1)	20(1·2)*
Thrombus uPA	—	5·7(4·4)	5·5(3·1)	14·7(7)	34(9·8)†
IVC thrombosed tPA	40·4(6·2)	28(7·1)	27(8·6)	101(34)	86(22)
IVC control tPA	40·4(6·2)	30(7·9)	61(17·3)	109(33)	96(25)
IVC thrombosed uPA	3·9(0·6)	6·2(1·5)	6·3(2·1)‡	9·2(1·6)	9·9(4·6)
IVC control uPA	3·9(0·6)	6·7(1)	11·7(3)	10·3(1·9)	8·2(1·9)

Values are mean(s.d.) expressed in units per g wet tissue $^*P < 0{\cdot}01$ *versus* 1 h $^\dagger P < 0{\cdot}03$ *versus* 1 h $^\ddagger P < 0{\cdot}05$ *versus* 2 days IVC control uPA

Both tPA and uPA production in the vein wall were significantly impaired in the presence of overlying thrombus. There was a marked increase in thrombus uPA content as organization proceeded uPA has only recently been found in blood vessels but has not previously been implicated in thrombolysis. It is evidently produced during the late, organization phase of thrombus breakdown

von Willebrand factor in atherosclerotic vascular disease

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Myocardial infarction (MI) and peripheral vascular disease (PVD) are common in atherosclerosis in which endothelial injury and thrombosis are important factors in pathogenesis. The von Willebrand factor antigen (vWFAg) is released by damaged endothelium and mediates platelet adhesion and aggregation

Serum vWFAg was measured by enzyme-linked immunosorbent assay in non-diabetic patients with PVD, 6 weeks after MI, and healthy hospital staff as controls; all were matched for smoking. Data were analysed by the Mann-Whitney *U* test and analysis of variance

Mean(s.d.) vWFAg in 69 controls was 89(32) units dl^{-1} compared with 142(38) units dl^{-1} in patients with PVD ($P<0.001$) and 125(38) units dl^{-1} in 38 patients following MI ($P<0.02$) These differences were influenced by hypertension (blood pressure >140/90 mmHg) and hyperlipidaemia (cholesterol $>7\,mmol\,l^{-1}$) In 37 patients with PVD and either hypertension ($n=33$) and/or hypercholesterolaemia ($n=16$), mean(s.d.) vWFAg was 136(36) units dl^{-1}, and was no higher than in 31 patients with PVD without these risk factors at 149(40) units dl^{-1} In ischaemic heart disease (IHD), mean(s.d.) vWFAg in 17 patients with these risks (hypercholesterolaemia, $n=9$; hypertension, $n=8$) was 148(35) units dl^{-1} compared with 102(27) units dl^{-1} in 19 patients without such risks ($P<0.001$).

The level of vWFAg was increased irrespective of hypertension and/or hypercholesterolaemia in PVD, but in IHD was raised only with these risk factors. A different pathophysiology may be involved in a proportion of patients with MI

Assessment of iloprost-treated femorodistal graft thrombogenicity with ^{111}indium-labelled platelets

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The carbacyclin derivative iloprost, a stable prostacyclin analogue, has a protective action following bolus infusion during femorocrural reconstruction for critical leg ischaemia. *In vitro* studies suggest that iloprost may exert this effect through platelet antiaggregatory properties mediated via raised intracellular adenosine 3',5'-cyclic monophosphate levels A prospective randomized controlled trial was carried out to investigate effects of iloprost on femorocrural graft thrombogenicity *in vivo*

Eighteen patients undergoing femorocrural saphenous vein bypass for critical ischaemia received 3 μg iloprost or placebo, infused into the graft via an unligated side branch over 2 min Autologous platelets labelled with ^{111}In-oxine were injected on the second day after operation Digital γ camera images of both legs were obtained at 4, 24 and 48 h after injection Graft thrombogenicity was calculated using the ratio of counts over the graft to those over the contralateral reference limb Thrombogenicity indices (TIs) were obtained from the line of best fit through the ratios, placed by linear regression analysis.

Non-parametric Wilcoxon analysis revealed no significant difference between TI in treated (median 0·16 (range 0.04–0.23)) and untreated (median 0.13 (range 0.05–0·27)) grafts. These results suggest that beneficial effects of iloprost following femorocrural reconstruction are unlikely to be due to modulation of platelet aggregation and adherence to graft endothelium.

Salvaged blood and washed red cells in elective aortic surgery

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Autotransfusion techniques are becoming more widely accepted, however, salvaged blood may contain high levels of mediators that have been linked with the development of postoperative lung and renal damage. This study investigated the quality of salvaged blood and washed red cells obtained by a Haemonetics Cell Saver in 16 patients undergoing aortic reconstruction

Levels of free haemoglobin (Hb), linked with renal damage after operation, were measured using a tetramethylbenzidine assay Thromboxane B_2 (TxB_2) and leukotriene B_4 (LTB_4) were measured using an enzyme immunoassay, and activation of alternative (C3-properdin) and classical (C1s-C1 inhibitor) complement pathways was assessed using an inhouse enhanced chemiluminescence assay. These mediators have all been linked with lung damage after operation.

	Free Hb ($g\,l^{-1}$)	TxB_2 ($pg\,ml^{-1}$)	LTB_4 ($pg\,ml^{-1}$)	Classical complement (units ml^{-1})	Alternative complement (units ml^{-1})
Salvaged blood	3.76(0.61)	2161(980)	306(112)	2.64(0.57)	13.32(8.93)
Washed cells	1.01(0.09)*	243(80)*	24(6)*	0.42(0.08)*	0.43(0.09)*

Values are mean(s.d.) $^*P<0.05$ (Wilcoxon signed rank test)

Salvaged blood contains high levels of free Hb, TxB_2, LTB_4 and complement activation However, these levels are all markedly reduced by washing Therefore, care should be taken when reinfusing large volumes of salvaged blood that has not been washed as such blood may contribute to lung and renal dysfunction after operation.

Low molecular weight heparin with or without graduated elastic compression in deep vein thrombosis prophylaxis after elective hip replacement

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In this study 78 patients (38 men, 40 women; mean age 69.2 (range 53–96) years) who underwent elective total hip replacement were randomized into three groups. control (group 1), low molecular weight heparin (LMWH – enoxaparin 40 mg day^{-1}) (group 2) and LMWH, with graduated elastic compression (TED stockings) on days 8–12 (group 3)

All patients underwent bilateral ascending venography on days 8–12. Group 1 received placebo injections The venograms were reported blind by an independent panel of three radiologists

An independent panel of sequential assessors stopped entry in group 1 when a total of 45 patients had been admitted according to ethics committee directives.

The incidence of deep vein thrombosis (DVT) was 93 per cent in group 1, 37.5 per cent in group 2 and 25 per cent in group 3 ($P<0.001$ group 1 *versus* 2 or 3, χ^2 test) The incidence of proximal DVT was 57 per cent in group 1, 28 per cent in group 2 ($P=0.057$) and 12·5 per cent in group 3 ($P<0.002$).

The results indicate that LMWH and LMWH with graduated elastic compression reduce the overall incidence of postoperative DVT significantly and that LMWH with graduated elastic compression appears to be more effective in reducing proximal DVT than LMWH alone

Preservation of neutrophil antimicrobial function after laparoscopic surgery

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Immunological dysfunction after surgical trauma exposes patients to the risk of postoperative sepsis. Polymorphonuclear neutrophil (PMN)-derived hypochlorous acid (HOCl) is the major immunological mechanism against bacterial and fungal infections Laparoscopic techniques that minimize surgical trauma may reduce stress-related immunological dysfunction This study therefore sought evidence of PMN HOCl generation dysfunction in 26 patients undergoing major resection. Patients were prospectively studied and underwent either open operative procedure (Op) ($n=12$) or laparoscopic procedure (Lap) ($n=14$) The two groups were comparable for age, sex and type of surgical procedure and no patient developed significant postoperative sepsis. PMNs were isolated (density-gradient centrifugation) from peripheral blood samples harvested before operation on days 1 and 6. The kinetic profile of HOCl generation was measured from isolated PMN by 5-thionitrobenzoic acid oxidation (spectrophotometer 412 nm)

	Time (min)				
	5–10	11–15	16–20	21–25	26–30
Before operation	0.27(0.04)	0.61(0.05)	0.63(0.04)	0.60(0.04)	0.53(0.03)
Op (day 1)	0.14(0.03)*	0.42(0.06)*	0.42(0.05)*	0.41(0.04)*	0.38(0·04)*
Before operation	0.24(0.05)	0.58(0.06)	0.58(0.05)	0.51(0.05)	0.47(0.04)
Lap (day 1)	0.23(0.04)	0.54(0.07)	0.57(0.06)	0.50(0.05)	0.49(0.04)

Values are mean(s.e.m.) PMN HOCl expressed in nmol per 10^6 PMNs per 5 min $^*P<0.05$ *versus* before operation (ANOVA)

HOCl generation returned to normal in both groups by day 6 The significant depression in PMN HOCl generation seen at day 1 following open surgery was not seen in laparoscopic surgery These data suggest that, during laparoscopic surgery, PMN antimicrobial function is preserved

Effect of simulated rapid gastric emptying on the lower oesophageal sphincter

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Patients with gastro-oesophageal reflux have been shown to have abnormal gastric motility. The influence of duodenal responses to changes in gastric emptying patterns on the lower oesophageal sphincter was explored.

Fourteen fasted subjects (ten men, four women, median age 28 (range 24–51) years) were intubated with a nasoduodenal tube and a water-perfused manometry catheter. Lower oesophageal sphincter pressure vector volumes and sphincter length were calculated from station pull-through manometry in the basal state and following 15-min duodenal instillations with 15 per cent dextrose at 3 ml min^{-1}, 15 per cent dextrose at 9 ml min^{-1} and isotonic saline at 9 ml min^{-1}. Ethical committee approval was obtained.

There was no significant difference between median (interquartile range) lower oesophageal sphincter pressure vector volumes in the fasted state (10 073 (5984–13 108) mmHg mmHg mm) and those following dextrose at 3 ml min^{-1} (10 251 (4956–12 552) mmHg mmHg mm) or saline at 9 ml min^{-1} (7869 (6467–14 773) mmHg mmHg mm). Dextrose at 9 ml min^{-1} caused a large reduction in vector volume (1247 (282–2527) mmHg mmHg mm ($P<0·01$, Wilcoxon signed rank test).

Total length of sphincter in the fasted state (median 40 (range 30–50) mm) fell after duodenal dextrose at 9 ml min^{-1} (median 30 (range 20–40) mm) ($P<0·05$, Wilcoxon signed rank test). The abdominal length of sphincter also fell but this was not significant.

A volume of 15 per cent dextrose instilled into the duodenum at supranormal rates causes a significant fall in lower oesophageal sphincter pressure vector volumes and total length of sphincter. These results may explain the common coexistence of symptoms of early rapid gastric emptying of liquids and gastro-oesophageal reflux.

Proliferating cell nuclear antigen in Barrett's epithelium

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Columnar-lined (Barrett's) oesophagus is a premalignant condition. Dysplastic change is an indicator of its malignant potential. This potential is mirrored in proliferative activity. Proliferating cell nuclear antigen (PCNA) is synthesized in the late G1 and S phase of the cell cycle, the proliferative phase. PCNA may be identified by the monoclonal antibody PC10 in archival pathological material. PCNA counts were recorded in a total of 70 patients with Barrett's oesophagus. 18 having specialized intestinal metaplasia, 24 dysplasia, nine regenerative change and 19 malignant change. A total of 1200 cells were counted in each specimen: 600 surface and 600 glandular epithelial cells. PCNA was present or absent and results were expressed as mean(s.e.m.) proliferation index (positive cells per 100 counted).

	Proliferation index		
	Surface cells	Glandular epithelium	Tumour cells
Benign	6·8(1·2)	7·9(1·5)*‡	—
Regenerative	16·4(5·5)	23·3(5·9)	—
Dysplastic	22·3(3·2)	34·7(3·2)	—
Mild/moderate	18·4(3·0)	31·1(2·6)	—
Severe	32·3(7·1)	43·5(7·4)	—
Malignant	—	—	59·0(4·3)†

Values are mean(s.e.m.) *$P=0·001$ *versus* dysplastic, †$P=0·009$ *versus* dysplastic; ‡$P=0·0001$ *versus* malignant (Wilcoxon rank sum test)

Increasing PCNA scores correlated with a greater proliferative capacity in both cell groups. While intergroup variation may limit the prognostic ability of PCNA, it may have a role in the interpretation of change in dysplastic epithelium.

Assessment of pain after laparoscopic cholecystectomy and minicholecystectomy

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Laparoscopic cholecystectomy (LC) is claimed to result in less postoperative pain than open cholecystectomy, but this claim has never been documented objectively. This randomized study assessed pain and analgesia requirements after LC ($n=40$) and minicholecystectomy (MC) (5–7-cm subcostal incision, $n=42$). Demographic data and the conversion rate to standard cholecystectomy were similar in both groups. Linear analogue pain scores (LAPSs) were completed after explanation by a single interviewer 1, 2, 10 and 30 days after operation. Morphine was given by a patient-controlled analgesia (PCA) device for the 24 h immediately after operation. On days 10 and 30 after operation, wound discomfort was assessed on a four-point descriptive scale for five different physical movements to give a total discomfort score (DS) of 0–15.

	MC	LC	P*
LAPS (day 1) (0–100 mm)	50 (40–76)	40 (30–55)	0·024
LAPS (day 2) (0–100 mm)	40 (21–60)	22 (10–45)	0·008
PCA over 24 h (mg morphine)	40 (20–50)	27 (17–44)	0·108
DS (day 10) (0–15)	5 (2–9)	2 (0–6)	0·010
DS (day 30) (0–15)	0 (0–3)	0 (0–1)	0·76

Values are median (interquartile range). *Mann–Whitney U test

The difference in morphine consumption between LC and MC was significant ($P=0·036$) only after excluding conversions. Analgesia requirement and LAPS at 10 and 30 days were not significantly different. These data confirm that LC is less painful than minimal-trauma open cholecystectomy.

Octreotide (SMS) *versus* sclerotherapy for bleeding varices: preliminary results

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Recent studies have indicated that somatostatin is a safe effective treatment for the control of acute variceal haemorrhage. Since SMS (octreotide), a synthetic analogue of somatostatin, is relatively inexpensive compared with naturally occurring hormone, the aim of this study was to compare the efficacy of SMS with injection sclerotherapy (IS) in the control of acute variceal haemorrhage.

Forty consecutive patients admitted with endoscopically proven severe acute variceal haemorrhage were randomized to either IS ($n=20$) or a continuous infusion of SMS (50 μg h^{-1}) ($n=20$) for 48 h. The aetiology of the portal hypertension was similar in the two groups as was the distribution of the patients among the categories of Child's classification. Overall control of bleeding was achieved in 18 of 20 patients receiving SMS and 18 of 20 randomized to IS (relative risk of rebleeding while receiving SMS compared with IS 1 (95 per cent confidence interval 0·4–2·7)).

SMS was equally effective as IS in controlling acute variceal haemorrhage in patients with mild, moderate and severe disease and those actively bleeding at the time of diagnostic endoscopy. The mortality rate was not significantly different between the two groups of patients (relative risk of dying while receiving SMS compared with IS 1 (95 per cent confidence interval 0·49–2·05)). No major complications were observed with either treatment.

The results of this trial suggest that SMS is a safe and effective stop-gap treatment for the control of acute variceal haemorrhage and may be as efficacious as IS, although at this stage a type 2 error cannot be excluded.

Cholecystokinin is a physiological mediator in the brain of satiety induced by gastric distension

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Cholecystokinin (CCK) has been implicated as a central mediator of satiety. Gastric distension, a satiety signal of importance in limiting meal size, causes CCK release from the lateral hypothalamus. This study investigated the effect of intracerebroventricular (ICV) injection of the CCK-B receptor antagonist L-365 260 on satiety induced by balloon gastric distension (BGD) and small bowel nutrient infusion in dogs

Five dogs were prepared with oesophageal and gastric fistulas and cerebroventricular guides that allowed intermittent cannulation of the lateral cerebral ventricle. After ICV injection of L-365 260 (13 μg kg^{-1}) or control (glycerol–polyethylene glycol 400–0·9 per cent saline) the dogs underwent BGD or small bowel nutrient infusion, which reproduced the normal volume of gastric distension and rate of entry of food into the small bowel after a meal, respectively Satiety was measured at the end of each experiment by sham feeding with the oesophageal fistula open and the distal oesophagus obstructed with a gauze ligature.

	Volume sham fed (ml per 10 min)	
	BGD	Small bowel nutrient infusion
ICV control	1300(392)	603(367)
ICV L-365 260	2560(270)*	680(404)

Values are mean(s.e.m.) *$P<0·05$

It is concluded that central CCK receptor antagonism abolishes satiety induced by gastric distension, that ICV L-365 260 had no effect on satiety induced by the presence of nutrients in the small bowel and that CCK is a physiological mediator in the brain of satiety induced by gastric distension

Pharmacological reduction of the systemic effects of exercising ischaemic muscle

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Most patients with intermittent claudication are treated by exercise Muscle ischaemia induced by exercise causes systemic vascular endothelial injury, resulting in increased permeability manifested as a measurable increase in urinary albumin excretion Repetitive systemic vascular endothelial injury leads to accelerated atherogenesis and may explain the high mortality rate of claudicants. If exercise is to remain the mainstay of therapy then the systemic effects of repetitive muscle ischaemia must be prevented. A xanthine derivative, oxpentifylline, prevents systemic vascular endothelial injury in animal models. A double-blind placebo-controlled crossover trial was undertaken to determine the effect of oxpentifylline on exercise-induced systemic vascular endothelial injury in 20 claudicants Albumin.creatinine ratio (ACR) to account for differences in urine volume was measured before and after standardized exercise and after 1 week of treatment with either placebo or active drug The ACR differences at 1 h after exercise and before exercise using Wilcoxon scores (rank sums) are given below

		Median ACR		
Group	*n*	Period 1	Period 2	Sum of rank difference
Oxpentifylline–placebo	10	0·039	0·076	135*
Placebo–oxpentifylline	10	0·152	0·063	75*

*$P<0·03$ (Wilcoxon two-sample test)

Pharmacological reduction of the systemic effects of muscle ischaemia is possible and may be beneficial in survival

Poor prognosis of proximal compared with distal gastric cancer is not a function of tumour proliferation

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A new monoclonal antibody to proliferating cell nuclear antigen (PCNA), PC10, was used to study the role of regional variations in tumour proliferation on the differing prognosis of lesions of the proximal and distal stomach

Archive material from 90 gastric cancers resected between 1980 and 1990 was available. The most representative sections were stained for PCNA using a standard three-layer immunohistochemical technique and an index (percentage of dividing cells) derived from a count of 1000 cells from eight different tumour areas

There was a negative correlation between PCNA index and survival ($r=-0·37$, $P<0·05$). The 5-year survival rate of patients with tumours of high PCNA index (greater than the mean value) was 15 per cent and of low index 27 per cent

There was no significant difference in the PCNA index of tumours arising in different parts of the stomach.

Site	*n*	Mean(s d.) PCNA index	5-year survival rate (%)
Oesophagogastric junction	17	48·5(15·2)	17
Cardia	14	41·5(12·9)	13
Gastric body	22	44·3(13·3)	12
Antrum	25	47·8(12·6)	32
Linitis plastica	8	38·8(17·5)	0

It is concluded that, while tumours with a high proliferation index are associated with a worse prognosis, factors other than variations in proliferation must account for the difference in behaviour of proximal and distal gastric cancers.

Surgical significance of neutrophil phosphatidylinositol glycan-tailed receptors

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The neutrophil receptor for immunoglobulin G, known as CD16, is anchored to the cell membrane by a phosphatidylinositol glycan (PIG)-tail. Neutrophil activation cleaves this tail, releasing soluble CD16 Individuals with high levels of neutrophil CD16 expression secrete proportionally more receptor following neutrophil activation than low expressors This, with the knowledge that defective PIG-tail anchorage increases circulating soluble CD16 levels and a predisposition to bacterial infections, led the authors to examine neutrophil CD16 expression in surgical patients Flow cytometric measurements were made in whole blood from 38 patients undergoing major surgery Twelve patients developed postoperative sepsis

	Preop	Day 1	Day 3	Day 5	Day 7
Uncomplicated	34·2(3·1)	38·4(2·7)	41·9(3·6)	31·4(6·5)	33·1(3·3)
Sepsis	41·3(6·9)	47·2(5·9)	45·1(6·0)	46·4(8·9)	40·8(5·9)

Values are mean(s e m) of mean channel fluorescence

As neutrophil CD16 expression was significantly higher in the group with sepsis ($P<0·05$, two-way ANOVA), the impact of surgery on intracellular CD16 stores was assessed in a further 12 patients by measuring CD16 expression in neutrophils from both whole blood and density gradient (DG)-separated neutrophils (this maximally mobilizes CD16 stores) and on the ability of tumour necrosis factor (TNF) and lipopolysaccharide (LPS) to cleave neutrophil CD16

	Whole blood	Baseline (DG)	TNF (DG)	LPS (DG)
Preop	39·2(4·8)	414·4(81·4)	345·1(76·1)	377·2(65·3)
Day 1 postop	43·4(6·9)	264·2(36·8)*	203·4(25·7)*†	225·8(30·5)*†

Values are mean(s e m) of mean channel fluorescence *$P<0·05$ *versus* preoperative †$P<0·02$ *versus* own baseline (Student's *t* test)

Thus CD16 stores are depleted after operation Only at this time do neutrophil activators produce significant cleavage of membrane-bound CD16 It is concluded that neutrophil expression and release of soluble CD16 from its PIG-tail is important in the aetiology of sepsis after surgery

Pulmonary function after laparoscopic cholecystectomy

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Upper abdominal surgery is associated with a significant reduction in postoperative pulmonary function and oxygen saturation. This randomized study assessed pulmonary function and oxygen saturation after laparoscopic cholecystectomy (LC) ($n = 40$) and minicholecystectomy (MC) (5–7-cm subcostal incision, $n = 42$). Demographic data and the conversion rate to standard cholecystectomy were similar in both groups. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate (PEFR) were measured before operation and 1 and 2 days after operation.

	MC	LC	P*
FVC			
24 h	52	63	0·036
48 h	70	79	0·035
FEV_1			
24 h	49	61	0·019
48 h	71	77	0·068
PEFR			
24 h	45	63	0·0026
48 h	60	75	0·012

Values are median percentage of preoperative value. *Mann–Whitney *U* test

After operation O_2 saturation was monitored continuously for 24 h using a pulse oximeter. Supplemental O_2 was given only if O_2 saturation fell below 86 per cent. Oxygen supplementation was required in 22 patients in the MC group (52 per cent) compared with ten (25 per cent) in the LC group ($\chi^2 = 6·46$, $P = 0·01$). Despite the longer median anaesthetic time (LC 92 min *versus* MC 70 min, $P < 0·0001$) and the cardiorespiratory effects of CO_2 pneumoperitoneum, LC results in better postoperative pulmonary function and O_2 saturation than MC and may, therefore, reduce the risk of pulmonary complications in high-risk patients.

Effect of L-arginine on immune suppression and catabolism of obstructive jaundice

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The immunostimulatory actions of L-arginine in trauma and sepsis are well documented. The increased operative mortality and morbidity rates in jaundiced patients are partly due to immune suppression and cachexia. It was hypothesized that dietary supplementation with arginine would abrogate the catabolic and immune suppressive effects of obstructive jaundice.

Male Wistar rats ($n = 16$; weight 375–480 g) underwent bile duct ligation and randomization to two groups. The experimental group received 1·8 per cent arginine-supplemented drinking water. Controls received isonitrogenous glycine-supplemented water. After 3 weeks delayed-type hypersensitivity (DTH) response to dinitrofluorobenzene was assessed. Body-weight, food and fluid intake were recorded.

	DTH (%)	Weight loss (%)	Food intake (g)
Arginine	23·9(2·7)*	7·8(1·2)*	414(16)*
Glycine	9·4(2·1)	14·8(1·4)	360(13)

Values are mean(s.e.m.) *$P < 0·05$ (Student's *t* test)

These results demonstrate that dietary arginine supplementation enhances immune function and decreases cachexia in obstructive jaundice, although the mechanism requires further study. Dietary arginine supplementation may improve immune function in jaundiced patients.

Correlation between mutations of the p53 protein and antibody staining

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Abnormalities of the p53 tumour suppressor gene are the commonest genetic alteration in a range of common tumours (e.g. breast, colon, lung). The majority of the mutations identified so far lie within exons 5–8 in a mutation 'hot-spot' region.

The p53 protein is involved in cell cycle regulation and normally has a short half-life. Immunohistochemical techniques using p53 antibodies demonstrate staining in carcinoma cells, representing detection of an abnormally stable p53 protein. Examination of the gene at the DNA or RNA level detects specific mutations that may result in an abnormal protein.

DNA was extracted from 81 fresh breast carcinomas and examined for p53 mutations in exons 5–8 using the polymerase chain reaction–single strand conformational polymorphism (PCR–SSCP) technique. Band shifts signifying mutations were detected in 13 patients.

Immunohistochemical staining for p53 protein (using CM-1 polyclonal antibody) was performed on formalin-fixed paraffin-embedded tissue from the same tumours. Strong positive staining was detected in ten of 77. Positive staining was associated with a PCR–SSCP-detected mutation in only two patients.

This interesting result suggests that staining for p53 protein may correspond to mutations outside the region examined or with abnormalities of the transcriptional regulator of the p53 gene.

Platelet activation *in vivo* during exposure to acute hand vibration

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Exposure of the hand to acute vibration causes a decrease in digital blood flow; this study investigated the hypothesis that vibration-induced platelet activation is responsible. One recognized marker of platelet activation *in vivo* is β-thromboglobulin. Circulating platelet aggregates may result from intravascular platelet activation. This study looked at 38 subjects: ten (eight male, two female) normal, 14 (two male, 12 female) with primary Raynaud's disease and 14 (all male) with vibration-induced white finger (VWF). A previbration venous blood sample was taken and the subject's hands were then vibrated at 120 Hz with 0·15-mm displacement for 1 min after which a second venous blood sample was taken. The β-thromboglobulin levels and circulating platelet aggregate (CPA) ratios were measured.

	β-Thromboglobulin (ng ml^{-1})		CPA ratio	
	Before vibration	After vibration	Before vibration	After vibration
Control	35·5(17–65)	47·5(24–91)*	0·98(0·91–1·01)	0·96(0·91–1·03)
Raynaud's	50·5(27–232)	49·5(30–254)	0·94(0·86–1·03)	0·94(0·84–0·99)
VWF	44(28–255)	47·5(36–257)*	0·97(0·79–1·02)	0·98(0·87–1·03)

Values are median (range). *$P < 0·005$ *versus* before vibration (Wilcoxon signed rank test)

These results indicate significant platelet activation occurs *in vivo* in response to acute hand vibration in control subjects and in patients with VWF. Ultimately, repetitive vibration-induced platelet activation may be important in the pathogenesis of VWF.

Regulation of fibroblast proliferation by mononuclear cells in the normal wound

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Fibroblasts are fundamental to successful wound repair. This study determined which wound elements are responsible for controlling fibroblast proliferation by use of a thymidine incorporation assay. Fibroblasts obtained from wounds at different times after injury displayed alterations in proliferative responses.

Wound fluid (WF) obtained from 7- and 10-day-old wounds caused significant inhibition in proliferative responses of normal dermal fibroblasts (NF), while 3- and 5-day WF had no significant effect. Wound mononuclear cells (WMNC) from 10-day-old wounds were cocultured with NF. Both crude and predominantly macrophage wound cell populations caused significant inhibition of proliferation while neither of the predominantly lymphocytic populations had any effect.

	NF	5-day WHF	7-day WHF	10-day WHF
WHF proliferation (c p m) ($n=9$)	15 641(132)	16 700(1273)	22 887(1888)*	12 949(1955)*

	Control	With 3-day WF	With 5-day WF	With 7-day WF	With 10-day WF
NF with WF (c p m) ($n=9$)	14 101(432)	9076(365)	9570(437)	538(342)*	339(14)*

	Control	With WMNC	With M	With L 1	With L 2
NF with WMNC (c p m) ($n=9$)	17 433(1019)	10 849(695)*	7769(54)*	20 833(4482)	16 030(5151)

Values are mean(s e m) WHF wound fibroblasts, M macrophage, L, lymphocyte *$P<0·05$

Wound macrophages recovered from 10-day-old wounds and their conditioned medium inhibit fibroblast proliferation A factor that causes a similar inhibition of fibroblast proliferation appears in the wound 5–7 days after injury.

Peripheral lymph node analysis as an indicator of host reactivity in small bowel transplantation

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In small bowel transplantation across an allogeneic barrier it has been established that there is extensive cell migration from graft to host as well as host infiltration of the grafted small bowel This study was undertaken to investigate whether the two-way cellular migration is in part physiological or driven solely by immunological responses and whether host cell reactivity against the graft in rejection affects the level of graft cells present in host tissues

Three groups of rats ($n=16$ per group) were transplanted with vascularized Thiry–Vella loops of jejunum and ileum. group 1 – PVG to DA, no immunosuppression, group 2 – PVG to DA, cyclosporin $15 \mathrm{mg\,kg^{-1}\,day^{-1}}$, and group 3 – (DA × PVG) to DA, cyclosporin $15 \mathrm{mg\,kg^{-1}\,day^{-1}}$.

The cyclosporin dose suppressed rejection in groups 2 and 3 In group 3 there was no immune stimulus provoking cell migration from graft to host Graft cell infiltration of host peripheral lymph nodes (PLNs) was assessed at serial time points using immunohistology with strain-specific monoclonal antibodies (PVG, OX27; DA, MN4). Infiltrating cells were expressed as a percentage of the total cell count. Rejection was assessed by conventional histology

	Infiltration of host PLNs by graft cells (%)			
	Days 1–2	Days 3–4	Days 5–6	Days 7–8
Group 1	3	5	2	0
Group 2	2	5	13*	53*
Group 3	3	7	15*	20*

*$P<0·05$ *versus* group 1 (Mann–Whitney *U* test)

Graft cell infiltration of host PLNs increased progressively in groups 2 and 3 but fell in group 1 in line with the onset of rejection at day 5 Cell trafficking to the host PLNs is partly physiological but the number of graft cells within the recipient lymphoid tissues may provide a marker of host reactivity and a means of monitoring rejection in small bowel transplantation.

Extended liver preservation in University of Wisconsin solution

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Extended cold liver storage in University of Wisconsin (UW) solution has greatly facilitated liver transplantation However, recent reports suggest extended storage may be associated with increased non-anastomotic biliary stricturing

A review of 229 consecutive adult patients with chronic liver disease undergoing transplantation between April 1988 and December 1991 has been undertaken to assess the impact of extended storage

Organ perfusion at retrieval was with 1 litre UW solution at 4°C via the portal vein and 3 litres Marshall's solution through the aorta After removal, the hepatic artery, portal vein and biliary system were flushed with 250 ml UW solution. Grafts were arbitrarily allocated to group 1 with storage time < 12 h or group 2 with storage time > 12 h.

	Group 1	Group 2
No. of grafts	114	115
Median (range) preservation time (h)	9 (2–12)	14·5 (12–27)
Major morbidity episodes	15	22
Primary non-function	3	3
Hepatic necrosis	2	4
Hepatic artery thrombosis	4	6
Biliary strictures		
Non-anastomotic	3	3
Anastomotic	3	6
Median (range) ASAT (units $\mathrm{l^{-1}}$) at 3 months	23 (9–190)	19 (10–91)
Patient survival at 1 year (%)	80	79
Graft survival (%)	73	73

ASAT, aspartate aminotransferase *P* not significant

Although a trend appears to suggest increased morbidity with extended storage, there appears to be no evidence of an increase in biliary non-anastomotic stricturing These results suggest that UW solution can be used safely for extended periods of time

Comparison of University of Wisconsin solution with hyperosmolar citrate for vascular perfusion before human pancreatic islet isolation

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To determine the optimal vascular perfusate before islet isolation, 14 human pancreata were randomized to *in situ* perfusion with either University of Wisconsin (UW) solution ($n=7$) or hyperosmolar citrate (HOC) ($n=7$) Each pancreas was subsequently processed by collagenase digestion and islet purification on continuous linear density-gradients of bovine serum albumin.

Median (range) cold ischaemia times were 1·5 (0 5–4·0) h for the UW group and 2·0 (0·75–6 0) h for HOC Before purification the number of 150-μm islet-equivalents was 3909 (2335–18 653) $\mathrm{g^{-1}}$ with 87 (33–96) per cent cleavage index for UW, compared with 5919 (605–9572) $\mathrm{g^{-1}}$ with 84 (53–90) per cent cleavage for HOC The amylase contamination of a 60 per cent islet yield was 22 (1–60) per cent for UW and 25 (5–47) per cent for HOC There were no statistically significant differences between the two groups in any of these parameters (Mann–Whitney *U* test).

In conclusion, there is no advantage in the use of UW solution for *in situ* vascular perfusion of the pancreas before islet isolation if cold ischaemia time is short (<6 h). Indeed, the additional cost of UW solution makes HOC preferable in these circumstances

Hypochlorous acid in interleukin 2 induced capillary leak syndrome

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Hypochlorous acid (HOCl) generated by the respiratory burst of circulating neutrophils is cytotoxic to human tumour cells. Infusion of recombinant interleukin 2 (rIL-2) is thought to exert antitumour activity by stimulation of lymphokine-activated killer cells However, rIL-2 efficacy is dose-limited by the capillary leak syndrome (CLS) presumed to be mediated by tumour necrosis factor alpha (TNF-α) via priming of the neutrophil respiratory burst This study therefore sought evidence of neutrophil respiratory burst enhancement and TNF-α elaboration in five patients (eight treatment cycles, $n=8$), of whom two had malignant melanoma, two renal cell carcinoma and one colonic cancer, during 5-day therapeutic infusions of rIL-2 (3 units m^{-2} day^{-1})

The kinetic profile of HOCl generation was measured from isolated neutrophils by 5-thionitrobenzoic acid oxidation and plasma TNF-α by radioimmunoassay Body-weight significantly increased during the 5-day treatment, confirming clinically significant CLS (mean(s.e.m.) 76·6(1·7) kg baseline *versus* 84·0(1·3) kg on day 5, $P<0·05$, paired *t* test) TNF-α levels significantly increased on day 1 (mean(s.e.m.) 7·8(1·3) pg ml^{-1} baseline *versus* 53·9(10·1) pg ml^{-1} on day 1) and returned to baseline by day 5

	Mean(s.e.m.) HOCl (nmol per 10^6 PMNs)			
	10–15 min	15–20 min	20–25 min	25–30 min
Baseline	0·66(0·08)	0·55(0·06)	0·43(0·03)	0·29(0·02)
Day 1	1·08(0·08)*	0·84(0·06)*	0·62(0·04)*	0·41(0·04)*

PMN, polymorphonuclear neutrophil. *$P<0·05$ (ANOVA)

A significant elevation in neutrophil HOCl generation also occurred by day 1. This respiratory burst enhancement strongly links rIL-2 infusion with the CLS However, while modulation of this effect with HOCl scavengers suggests a means of modifying IL-2 toxicity, the neutrophil HOCl contribution to tumour cell death is unknown as yet

Amnion-derived growth factor stimulation of neochondrogenesis

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Human amnion lacks expression of the major histocompatibility antigens and has been used in wound healing and repair of various membranous defects, for example as a replacement for pelvic peritoneum

This study investigated the use of human amnion for resurfacing full-thickness complete articular defects in the knee joints of 149 rabbits. Cultured human amnion was transplanted into 33 rabbit knee joints after complete excision of articular cartilage from both the femoral and tibial surfaces. Various controls were used including no implants, poly-L-lactide film and amnion mesenchyme

Sequential follow-up, autopsy and serial histological analyses demonstrated that significant hyaline-like cartilage developed regularly at the human amnion–bone interface. This occurred from 6 weeks after operation, was prominent in the medial half of the joint, and maintained integrity under loading up to at least 1 year There was no overt evidence of rejection

Other experiments have shown that human amnion produces a growth factor capable of stimulating human and rabbit articular chondrocyte growth in culture and this appears to be the likely mechanism for the neochrondrogenesis observed with amnion resurfacing. This has considerable clinical potential in patients with arthritis because of the easy availability of human amnion

Lymphocyte activation in acute inflammation

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Traditional immunological doctrine associates acute inflammation with polymorph and chronic inflammation with lymphocytic infiltration Recent studies have demonstrated peripheral lymphopenia in a variety of acute inflammatory conditions, namely appendicitis, diverticulitis and pancreatitis. Selective memory T lymphocyte recruitment into the inflamed appendix has been demonstrated. Resting T lymphocytes do not express significant levels of interleukin 2 receptor (IL-2R) On activation, expression of IL-2R is upregulated and soluble IL-2R released

Lymphocyte counts and plasma levels of soluble IL-2R were measured in 29 patients before and 7 days after undergoing appendicectomy (eight gangrenous, 11 acutely inflamed and ten normal histology) Plasma IL-2R levels were significantly raised before operation in the gangrenous group (mean(s.d.) 1276(252) units ml^{-1} *versus* normal histology mean(s.d.) 607(140) units ml^{-1}, $P=0·01$) These levels correlated with the peripheral lymphocyte count ($r=0·54$, $P=0·02$) On day 7 plasma IL-2R levels had declined but remained greater than normal in the gangrenous group. T lymphocyte activation must occur in gangrenous appendicitis, the degree of activation correlates with the systemic lymphopenia. This supports the view that lymphocytes play a central role in acute inflammation

Signal-transducing oncogene *ras* and immunosuppression in squamous cell skin cancer

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Renal allograft recipients have a greater incidence of squamous cell carcinoma (SCC) of the skin than the general population The aetiology appears to be multifactorial and at the molecular level may involve mutations of the signal-transducing oncogene *ras*

To investigate the neoplastic progression of these lesions the incidence of mutations at K-*ras* codons 12 and 13 and H-*ras* codon 12 in SCC of immunosuppressed patients and appropriate controls was studied.

DNA was extracted from tumour biopsies of 18 transplant recipients (immunosuppressed group) (median age 51 years) and 20 age- and sex-matched controls (group 1) Further controls (group 2) (median age 78 years) more representative of the normal age of presentation were studied. Genomic DNA was amplified by the polymerase chain reaction using mismatched primers that introduce restriction sites capable of differentiating wild type and mutant oncogenes

Mutation	Immunosuppressed	Group 1	Group 2
H-*ras* codon 12	3 of 18	0 of 20	2 of 10
K-*ras* codon 12	1 of 18	0 of 20	1 of 20
K-*ras* codon 13	0 of 18	0 of 20	0 of 20

The incidence of *ras* mutations in SCC is low, however, the occurrence of mutations in the immunosuppressed patients resembles more closely the older control group than the age-matched group. This suggests that the molecular aetiology of SCC in the elderly may be similar to that in the immunosuppressed, whereas younger patients undergo a different neoplastic process

Expression of adhesion molecules in cadaveric kidney allografts

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A variety of adhesion molecules expressed on vascular endothelium potentially influence cellular infiltration into organ allografts but the relative importance of adhesion molecules in rejection is unclear

Expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), platelet endothelial cell adhesion molecule 1 (PECAM) and endothelial leucocyte adhesion molecule 1 (ELAM-1) in kidney allografts was assessed by immunocytochemistry in 45 biopsies from 42 patients with renal dysfunction Clinical diagnoses included acute rejection ($n=19$), chronic rejection ($n=6$), acute tubular necrosis ($n=3$), cyclosporin A toxicity ($n=5$) and non-immunological causes ($n=13$)

Expression of ELAM-1 was minimal in kidneys before transplant and only occasionally induced following transplantation In contrast, PECAM was uniformly expressed on capillary endothelium before and after transplantation and was not induced during rejection Before transplantation ICAM-1 was present on capillary endothelium and variably expressed on proximal tubules and glomerular epithelium, while VCAM-1 was detected on Bowman's capsule and occasionally on capillary endothelium There was a striking association between leucocyte infiltration and induction of both VCAM-1 and ICAM-1 in 19 of 25 patients with ongoing rejection. ICAM-1 was induced on proximal tubules while VCAM-1 was increased on proximal tubules and glomerular and capillary endothelium Little induction was seen in patients with non-immunological causes of dysfunction

Adhesion molecules ICAM-1 and VCAM-1 are strongly induced in rejecting grafts, suggesting that they are important in the pathogenesis of rejection

Acute-phase response and prediction of response to interleukin 2 therapy in colonic carcinoma

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Recombinant interleukin 2 (rIL-2) is being used to treat cancers but there is no reliable way of predicting responders to this treatment. This study evaluated the role of the acute-phase response as a predictor of response in patients undergoing treatment with rIL-2.

Twenty patients with metastatic colorectal cancer underwent constant infusion of rIL-2 (18×10^6 units m^{-2} day^{-1} for a total of 120 h) followed by injections of 5-fluorouracil (600 mg m^{-2}) and leucovorin (25 mg m^{-2}) given on three occasions at weekly intervals.

Serum levels of C-reactive protein (CRP), retinol-binding protein (RBP), α_1-antitrypsin (α_1AT) and transferrin (TF) were measured using rate nephelometry. The response to therapy was assessed by serial imaging according to Union Internacional Contra la Cancrum criteria.

Response of disease	CRP (mg l^{-1})	RBP (mg l^{-1})	TF (g l^{-1})	α_1AT (g l^{-1})
Progression	39·4*	37·5	2·6	2·69
Stasis	7·6	39·1	2·6	2·41
Partial	4·2	42·5	2·3	2·46
Complete	4·3	56·6	3·1*	1·96*

*$P < 0·01$ *versus* other response groups

These results show that acute-phase response is different in patients who respond to rIL-2 therapy; measurement of CRP before treatment allows identification of patients who will not respond to rIL-2 therapy.

Computerized vector analysis of normal and neoanal sphincter pressures

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The effect of configuration of the electrically stimulated gracilis neoanal sphincter on intra-anal canal pressures is unknown. This study was designed to assess the radial symmetry of intra-anal canal pressures measured at 0° (posterior), 45°, 90° (left), 135°, 180° (anterior), 225°, 270° (right) and 315° in ten patients with neoanal sphincters (eight women, two men; mean age 48 (range 18–77) years) and 12 normal controls (five women, seven men, mean age 56 (range 32–72) years). Pressures were measured using a manometry probe with eight ports 2 cm from the tip connected via eight water-perfused (1 ml min^{-1}) transducers to a computerized recording system. The probe was withdrawn from the anal canal at a constant rate of 0·25 cm s^{-1} during stimulation of the neosphincter in patients with a neoanus and during voluntary contraction of the anal sphincter in controls. The pressures recorded from each channel were subtracted from the mean for all channels, perfect symmetry of radial pressures would be denoted by zero difference.

Radial offset							
0°	45°	90°	135°	180°	225°	270°	315°
Controls (mmHg)							
0·0 (−10·5 to 36·8)	0·3 (−7·9 to 10·3)	−2·0 (−9·2 to 12·0)	−2·2 (−10·6 to 6·7)	−1·5 (−13·4 to 9·7	−5·2 (−15·9 to 5·3)	2·1 (−5·1 to 10·3)	−4·2 (−9·2 to 1·2)
Neosphincter (mmHg)							
1·3 (−14·3 to 11·8)	10·0 (1·55 to 23·0)*	17·0 (2·3 to 46·2)*	0·7 (−8·0 to 22·6)	−9·61 (−16·3 to −0·5)*	−14·7 (−24·3 to −6·0)*	−5·9 (−22·7 to 7·76)	−2·6 (−23·4 to 5·6)

Values are median differences (95 per cent confidence interval). *$P < 0·03$ *versus* controls (Wilcoxon signed rank test)

These data show that the normal anal sphincter exhibits near-perfect symmetry during voluntary contraction. The neoanal sphincter produces marked kinking of the anal canal as demonstrated in the significantly higher pressures at 45° and 90° and significantly lower pressures at 180° and 225°.

Adherent layer of colonic mucus in mucosal protection and inflammatory bowel disease

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Colonic mucosa is covered by a layer of adherent mucus gel whose thickness may be relevant to mucosal protection and the pathophysiology of colonic disease although this has not previously been determined.

In this study direct measurement was made on thick mucosal sections from fresh colectomy specimens. The gel layer was viewed transversely by phase-contrast illumination using an inverted microscope and readings made via an eyepiece graticule. Sections were taken from tumours and resection margins. A total of 47 specimens were measured: 28 from carcinomas, two diverticulitis, one appendiceal mass, 11 ulcerative colitis and five Crohn's colitis. Mean(s.e.m.) adherent mucus thickness is shown below.

	Non-IBD		Ulcerative colitis			Crohn's colitis		
Site	*n*	Thickness (μm)*	*n*	Thickness (μm)*	*P*†	*n*	Thickness (μm)*	*P*†
Right colon	7	116(21)	9	78(33)	0·166	4	261(36)	0·018
Left colon	12	126(16)	8	22(14)	0·001	5	281(28)	0·004
Rectum	12	143(16)	9	53(31)	0·011	4	341(55)	0·004

*Values are mean(s.e.m.). IBD, inflammatory bowel disease. †*Versus* non-IBD at same site (Mann–Whitney *U* test)

The adherent mucus layer in ulcerative colitis is significantly thinner and more variable than in non-IBD, with actively inflamed areas completely denuded of mucus. In Crohn's colitis the layer is significantly thicker.

Since the adherent mucus layer is the interface between lumen and mucosa these differences may indicate alterations pertinent to development or persistence of inflammation and differences between ulcerative colitis and Crohn's disease.

Anal intraepithelial neoplasia in women with cervical intraepithelial neoplasia

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There is increasing evidence of an aetiological role for human papilloma virus (HPV) type 16 in the aetiology of anogenital carcinoma. Although anal cancer is ten times less common than cervical cancer, tumours may occur metachronously in the same individual. Clinically identifiable premalignant lesions have been described in the anus and cervix. Women with cervical intraepithelial neoplasia (CIN) may be at risk for anal intraepithelial neoplasia (AIN). This study reports an investigation of the prevalence of AIN in women presenting with CIN and in controls. HPV DNA was sought from all biopsies using a polymerase chain reaction.

A series of 152 women presenting to a colposcopy clinic with severely dyskaryotic cervical smears were examined by complete anogenital colposcopy. Biopsy of cervical and anal lesions was performed to confirm the clinical diagnosis. A further group of 50 women (controls) undergoing laparoscopic sterilization also underwent colposcopy, anal colposcopy and biopsy.

Twenty-nine of 152 (19 per cent) of the study group had evidence of AIN histologically, 11 of these were AIN III. In the control group no patient had AIN ($P = 0·001$), although one patient in this group had CIN I and one had a cervical condyloma. HPV type 16 DNA was detected in 80 per cent of women with multifocal lesions. This study supports the hypothesis that women with CIN may be at risk for AIN and suggests that anal examination should become part of the routine assessment of these patients.

Occult faecal leakage in pruritus ani

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The aetiology of pruritus ani is undetermined. This study assessed 20 patients with pruritus ani (20 males, median age 43 years) without coexisting anorectal pathology and 12 controls (12 males, median age

39 years) using ambulatory anal sphincter electromyography (EMG) and anorectal manometry. In addition, anal mucosal electrosensitivity and rectal compliance were measured.

Upper anal canal sensitivity was poor (median 19·1 *versus* 6·5 mA for controls, $P<0{\cdot}003$) and rectal compliance low (median 2·5 *versus* 5 for controls, $P<0{\cdot}03$). Internal sphincter EMG frequency was abnormal (median 0·32 *versus* 0·44 Hz in controls, $P<0{\cdot}04$). Ambulatory anal pressures were normal (median 74 *versus* 91 cmH$_2$O for controls, $P>0{\cdot}1$).

Sampling episodes occurred at a median rate of 3 per h (4 per h in controls). Sampling was intermittently abnormal in patients with pruritus ani with rectal pressure increases of 20–60 cmH$_2$O (controls 6–20 cmH$_2$O, $P<0{\cdot}01$). Internal sphincter relaxation during these episodes was prolonged for periods of between 20 and 55 s (controls < 10 s).

Patients with pruritus ani have abnormal anal mucosal sensation and poor rectal compliance. The internal sphincter is neuropathic. These abnormalities combine to cause leakage during sampling.

New developments in predictive diagnosis for familial adenomatous polyposis

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Familial adenomatous polyposis (FAP) is an autosomal dominantly inherited condition in which affected individuals develop colorectal cancer. Predictive diagnosis in FAP provides a unique population in which interventional therapy to prevent colorectal cancer could be evaluated. In this report the results from an intragenic DNA polymorphism study have been evaluated for predictive diagnosis.

DNA from nine FAP families and paraffin-wax preserved tissue samples from seven deceased FAP family members were studied. For each DNA sample a 140-base pair segment from exon 11 of the gene was specifically amplified by a polymerase chain reaction (PCR). In five families the affected allele was identified, providing predictive diagnosis in 13 family members. In all seven preserved samples the DNA was successfully amplified and allele status established.

Intragenic probes overcome many of the limitations of previously used linked probes. PCR of preserved tissue DNA samples from deceased family members can be used to make this form of predictive diagnosis available to otherwise unsuitable FAP pedigrees. In all, 80 per cent of FAP families should now be suitable for this form of predictive diagnosis. Young family members identified as carrying the affected gene can now be entered into trials to try to prevent or delay the onset of colorectal neoplasia.

Abnormal hepatic cytochrome P4501A2 activity in familial adenomatous polyposis

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The hepatic cytochrome P4501A2 enzyme can activate carcinogens, which are then excreted in bile. Patients with familial adenomatous polyposis (FAP) have multiple premalignant adenomas in the small and large bowel. They are at high risk of colorectal and duodenal cancers. Studies of DNA adducts indicate that polyposis bile contains more carcinogens than does non-polyposis bile. Higher levels of cytochrome P4501A2 activity in patients with FAP might contribute to this excess load of carcinogens.

Cytochrome P4501A2 activity was therefore measured in 35 patients with FAP (21 male, 14 female) and 254 age-matched controls (125 male, 129 female). Cytochrome P4501A2 activity was measured from urine collected 8 h after oral administration of caffeine, measurement of urinary metabolites was by high-performance liquid chromatography. Cytochrome P4501A2 activity was given by the ratio of the urinary metabolites 5-acetylamino-6-amino-3-methyluracil plus 1-methyluracil plus 1-methylxanthine plus paraxanthine to caffeine.

Activity was significantly higher in patients with FAP (mean(s.e.m.) (range) metabolite ratio 190(36) (6–847)) than in controls (mean(s.e.m.) (range) 97(6) (8–608), $P<0{\cdot}05$, Mann–Whitney U test). Sex had no effect on enzyme activity. These results suggest that the hepatic metabolism of carcinogens is abnormal in patients with FAP.

Anorectal dysfunction in multiple sclerosis

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Bladder dysfunction in multiple sclerosis (MS) has been well described. Disturbances of anorectal function are common in this group of patients but have received little attention. The aim of this study was to define anorectal motor, sensory and peripheral nerve function in patients with MS with constipation and faecal incontinence and compare them with non-MS patients with faecal incontinence and normal controls.

The study was of 20 patients with MS (12 women, eight men, median age 46 (range 28–70) years), 66 with faecal incontinence (52 women, 14 men; median age 56 (range 28–87) years) and 39 controls (13 women, 26 men; median age 50 (range 20–85) years). Anal resting pressure, maximum squeeze pressure and functional anal canal length were measured using a 4-mm microballoon and a station pull-through technique, together with rectal and anal canal mucosal electrosensitivity (MES), pudendal nerve latencies and fibre density.

	MS	Faecal incontinence	Controls
Anal canal length (cm)	3 (2·5–5)*	3 (2–6)	4 (2–5)
Resting pressure (cmH$_2$O)	80 (40–120)†	45 (20–150)	100 (4–200)
Squeeze pressure (cmH$_2$O)	25 (0–90)‡	37·5 (0–190)	140 (50–400)
Fibre density	1·7 (1·1–2·6)§	2 (1·1–2·9)	1·45 (1–2)
Right pudendal latency (ms)	2 (1·5–3·4)	2·3 (1·8–4·1)	2 (1·5–2·9)
Left pudendal latency (ms)	2 (1·5–3·2)	2·2 (1·6–4·8)	2 (1·4–3·3)
Anal MES (mA)	6 (1·2–18)	7 (1·2–39)	4·35 (1·7–11·5)
Rectal MES (mA)	20·5 (9–53)	34·5 (10·4–87)	24·4 (4·7–67)

Values are median (range). *$P=0{\cdot}01$ *versus* control group, †$P=0{\cdot}0007$ *versus* faecal incontinence. ‡$P=0{\cdot}0001$ *versus* control group. §$P=0{\cdot}03$ *versus* faecal incontinence (Mann–Whitney U test)

It is concluded that patients with MS and anorectal symptoms have impaired sphincter function and no evidence of peripheral nerve dysfunction. These abnormalities may be explained by lesions sited in the conus medullaris or higher in the central nervous system.

In vitro modulation of tumour necrosis factor, interleukin 6 and prostaglandin E$_2$ by centoxin

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Centoxin binds endotoxin and thus should modulate the early mediators of the cytokine cascade, namely tumour necrosis factor (TNF), interleukin 6 (IL-6) and prostaglandin E$_2$ (PGE$_2$). Mononuclear cells from four healthy volunteers were separated using Ficoll–Hypaque/Percoll centrifugation and resuspended in RPMI–10 per cent AB serum. Then 2×10^5 cells were added to wells containing preincubated cocktails of centoxin (4, 40 or 400 μg ml^{-1}) and lipopolysaccharide (10 ng ml^{-1}). At 5 and 24 h supernatants were collected and assayed for TNF, IL-6 and PGE$_2$.

Centoxin suppressed TNF at both 5 and 24 h. Maximal inhibition was achieved with 40 μg ml^{-1} ($P<10^{-4}$). After 24 h 400 μg ml^{-1} was more effective ($P<2\times10^{-5}$). Significant inhibition of IL-6 occurred only at 5 h ($P<10^{-3}$). For all donors a significant trend in PGE$_2$ production was not identified. However, high absolute PGE$_2$ concentrations were associated with IL-6 inhibition in two donors at both 5 and 24 h. The opposite occurred in the remaining two volunteers.

Centoxin concentration (μg ml^{-1})	TNF		IL-6		PGE$_2$	
	5 h	24 h	5 h	24 h	5 h	24 h
4	68	79	105	94	137	111
40	28	55	69	88	215	124
400	29	35	78	115	107	174

Values are mean percentage production

Centoxin partially inhibits TNF production *in vitro*. IL-6 inhibition was less than expected and combined with PGE$_2$ may be important in influencing individual responses to centoxin.

Effect of intravenous sclerosants on renal function in the rat

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Previous studies have demonstrated that ethanolamine oleate (EO) results in platelet microembolization, which may account for systemic complications such as renal and pulmonary failure and bacteraemia. The aim of this study was to determine whether EO causes alterations in renal haemodynamics and function in the rat.

Organ blood flow was measured 1 and 24 h after intravenous administration of EO in two doses (0·025 or 0·05 ml per 100 g) to two groups of portal hypertensive rats, using the radiolabelled microsphere technique. Renal function was determined by plasma clearance of renal tubular agent Mag3. Intravenous EO resulted in a rapid fall in the platelet count (mean(s.e.m.) $822(36)\times 10^9\,l^{-1}$ to $668(50)\times 10^9\,l^{-1}$) that was associated with microscopic or macroscopic haematuria. Renal blood flow was not altered significantly after 1 or 24 h. However, renal function was significantly impaired ($P<0{\cdot}01$, Mann–Whitney *U* test) 24 h after EO administration in the group that received 0·025 ml per 100 g (mean(s.e.m.) 0·98(0·08) ml per min per 100 g) compared with controls (1·67(0·19) ml per min per 100 g) and was even more impaired in the group that received the higher dose (0·65(0·08) ml per min per 100 g).

These observations suggest that renal functional impairment after administration of EO in rats is not associated with alterations in kidney blood flow but may result from platelet microembolization.

Free radicals as a cause of lower limb oedema in femoropopliteal bypass grafting

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This study investigated the relationship of free radical-induced lipid peroxidation with lower limb swelling in femoropopliteal bypass grafting. Twenty patients undergoing femoropopliteal bypass had blood samples taken from the femoral vein before clamping the femoral artery, before and immediately after clamp release, and at 10-min intervals thereafter for 1 h. Levels of plasma malondialdehyde (MDA) and the lipid-phase antioxidant vitamin E were measured. Lower limb measurements were made daily to assess swelling.

A significant rise in mean(s.e.m.) MDA concentration occurred 40 min after releasing the clamp (573(82) pmol ml^{-1}) compared with just before clamp release (359(41) pmol ml^{-1}) ($P<0{\cdot}05$, ANOVA). There was a significant drop in mean(s.e.m.) vitamin E (5·68(0·28) to 5·29(0·28) μmol per mmol cholesterol, $P<0{\cdot}05$) at the time of peak MDA rise, suggesting an antioxidant effect. Those with significant swelling had a higher elevation of MDA (364(44) to 693(76) pmol ml^{-1}, $P=0{\cdot}0001$) compared with those with less than 10 per cent increase in initial limb volume (344(40) to 559(243) pmol ml^{-1}, $P=0{\cdot}25$).

These findings suggest that free radicals play a significant role in lower limb swelling in femoropopliteal bypass grafting.

Splanchnic hypoperfusion and organ failure in abdominal aortic aneurysm repair

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Sigmoid intramucosal acidosis is a good indicator of splanchnic hypoperfusion. This was correlated with endotoxaemia and the development of multiple system organ failure (MSOF) in elective abdominal aortic aneurysm repair.

Twenty-one patients undergoing aneurysmectomy had their sigmoid colonic intramucosal pH (pH$_i$) monitored using a silicone tonomitor. Samples were taken for plasma endotoxin and tumour necrosis factor (TNF) before operation, every 30 min during the operation, every 2 h for 12 h, every 4 h for 48 h and every 8 h thereafter until the fifth day. Sigmoid colonic pH$_i$ fell to $<7{\cdot}00$ in ten patients during or shortly after operation. Four of these ten patients developed diarrhoea, compared with none of 11 whose sigmoid pH$_i$ remained $>7{\cdot}00$. The highest endotoxin and TNF peak concentrations were significantly higher in the group with pH$_i$ $<7{\cdot}00$ (mean(s.e.m.) endotoxin, 112(24) *versus* 58(6) pg ml^{-1}, $P<0{\cdot}05$, TNF, 26(8) *versus* 7(2) pg ml^{-1}, $P<0{\cdot}05$). Two deaths occurred, both within the group with pH$_i$ $<7{\cdot}00$, one from MSOF caused by bowel infarction, the other from cardiac complications. It is concluded that splanchnic ischaemia leads to endotoxaemia and is associated with a higher incidence of morbidity and mortality following abdominal aortic aneurysm repair.

Measuring ischaemic muscle fatigue by a new method of assessing muscle ischaemia

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Conventional methods of assessing muscle ischaemia are unreliable. Ischaemic muscle fatigue is a function of blood supply, microcirculation and biochemical adaptation, and can be used to measure muscle ischaemia.

Resistance to fatigue of ankle flexors was assessed in 20 normal subjects, 20 patients with intermittent claudication and 20 patients with critical ischaemia. Initial isometric contractions of 5–10 N were induced by standardized electromyostimulation (pulse width 350 ms, frequency 6 Hz) over 5 min. Resistance to fatigue was expressed as a percentage of the ratio of the force of contraction at each minute interval to the initial force.

	Mean(s.e.m.) resistance to fatigue (%)				
	1 min	2 min	3 min	4 min	5 min
Normal	95(5)	101(7)	97(6)	99(7)	100(5)
Claudicants	67(19)	59(26)	56(24)	53(19)	51(18)
Critical ischaemia	20(12)	15(20)	12(12)	10(12)	10(7)

The difference between the groups at each time interval was significant ($P<0{\cdot}001$, Student's *t* test). In claudicants, individual mean variation on different days was less than 12 per cent. There was no correlation with ankle:brachial pressure index but a weak correlation with maximum walking distance ($r=0{\cdot}65$). This shows that muscle fatigue is highly reproducible, reflects the degree of ischaemia, and may be a useful method of assessing muscle ischaemia.

Muscle stimulation reduces human ischaemic muscle fatigue

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Ischaemic fast glycolytic muscle fibres fatigue more quickly than slow oxidative fibres. In animal models, nerve stimulation at a frequency occurring naturally in slow muscle fibre converts fast to slow fibres.

Percutaneous electromyostimulation was used to stimulate the right ankle flexors of nine healthy subjects. Stimulation parameters were 8 Hz and 350-ms pulse width to produce maximum tolerated contractions. Six subjects (group 1) were stimulated for 20 min, three times a day, and three (group 2) were stimulated for 1 h, once a day. Stimulation was for 4 days per week for 4 consecutive weeks. Resistance to fatigue was expressed as the ratio of the force of isometric contractions at 2 Hz at 5 and 10 min to the initial force, under tourniquet ischaemia. The left leg was used as control.

	Muscle resistance to fatigue	
	Before stimulation	After stimulation
Group 1		
5 min	54(28·7)	135(43·3)*
10 min	34·5(11·5)	53·6(22·9)†

Values are mean(s.e.m.) *$P<0{\cdot}01$; †$P<0{\cdot}05$ (Student's *t* test)

Muscle performance also improved in group 2 but this was not statistically significant. There was no change in the control leg. These results show that muscle stimulation reduces muscle fatigue under ischaemic conditions and may be beneficial in patients with intermittent claudication.

Intestinal haemodynamics following reperfusion and haemorrhage

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Bilateral hindlimb ischaemia and reperfusion leads to abnormal intestinal permeability, which may contribute to the development of multiple organ failure This is not the result of reperfusion-induced hypotension as haemorrhagic hypotension does not cause such damage This study investigated whether this difference was related to alterations in intestinal blood flow in 18 pentobarbitone-anaesthetized rats following 5 h anaesthesia ($n=6$), 3 h ischaemia and 2 h reperfusion ($n=6$), and, to control for reperfusion-induced hypotension, 3 h ischaemia and 2 h haemorrhagic hypotension without tourniquet release ($n=6$) (experiments approved by the Home Office) Mean arterial pressure and anterior mesenteric arterial flow by an electromagnetic flow probe were measured and resistance calculated as pressure divided by flow

	Baseline	1 h	2 h	3 h	4 h	5 h
Reperfusion						
Pressure (mmHg)	110.5(5.9)	117.2(3.8)	117.7(6.9)	116.5(5.1)	85.2(5.1)*	79.6(3.3)*
Flow (ml min^{-1})	14.6(1.7)	15.8(2.4)	14.2(1.7)	12.7(1.3)	6.8(0.8)*†	5.5(0.6)*†
Resistance	8.1(0.9)	8.1(0.8)	9.0(1.1)	9.6(1.1)	13.6(1.6)*†	15.3(1.6)*†
Haemorrhage						
Pressure (mmHg)	117(3.0)	123.9(2.0)	128.0(3.7)	124.6(2.5)	85.0(1.3)*	84.6(1.0)*
Flow (ml min^{-1})	13.2(1.3)	15.2(1.1)	15.5(1.6)	15.4(1.6)	8.1(1.1)*†	7.9(0.9)*†
Resistance	9.3(0.8)	8.4(0.6)	8.7(0.7)	8.6(0.8)	10.9(1.0)*†	11.5(1.1)*†

Values are mean(s.e.m.) *$P<0.05$ *versus* baseline (ANOVA), †$P<0.05$ *versus* baseline (Mann Whitney *U* test)

At 4 h there was a marked reduction in flow and an increase in resistance in both reperfusion and haemorrhage groups However, the reduction in flow was greater after reperfusion compared with haemorrhage (54 *versus* 39 per cent below baseline), the difference being due to a greater increase in resistance after reperfusion compared with haemorrhage (67 *versus* 17 per cent above baseline) ($P<0.05$, Mann–Whitney *U* test)

These results indicate reperfusion alters intestinal haemodynamics independently of hypotension, suggesting a possible humoral mechanism for abnormal intestinal permeability

Isolated perfusion of amputated human legs to investigate white blood cells in ischaemia

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There is now considerable evidence that white blood cells (WBCs) play a central role in the pathophysiology of critical ischaemia This study investigated WBC retention in the microcirculation using isolated perfused human legs.

Forty-one human legs were perfused immediately after amputation and shown to be haemodynamically stable for 50–260 (mean 164) min The perfusate used was a 4.1 per cent Krebs–dextran 110 solution that was oxygenated and pumped through the leg using a variable-speed peristaltic pump. When boluses of whole blood were injected there was a significant ($P<0.05$, Wilcoxon rank sum test) positive correlation between the percentage of injected WBCs and red blood cells (RBCs) collected in the venous effluent and the perfusion pressure. The increase in WBC trapping was significantly greater than the increase in RBC trapping at reduced perfusion pressure ($P<0\text{-}05$, Wilcoxon rank sum test) The cells that were trapped as the perfusion pressure was decreased could be retrieved by subsequently increasing the perfusion pressure

Deliberate activation of granulocytes before injection increased WBC retention associated with decreased perfusion pressure within the microcirculation. The additional retained cells after activation could not be retrieved by a period of high-pressure washout.

In conclusion, WBCs are retained within the human microcirculation at reduced perfusion pressure There are several mechanisms involved in WBC retention This supports the hypothesis that at least some of the microcirculatory changes associated with severe leg ischaemia are associated with WBC activation and possibly their inappropriate activation

Bacterial translocation during peroperative colonic lavage of the obstructed rat colon

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Peroperative antegrade colonic lavage is often performed before primary anastomosis in emergency colonic surgery The aim of this study was to determine the influence of colonic lavage on bacterial translocation from the obstructed colon

Forty female Wistar rats were studied in four groups (1) control ($n=10$), (2) non-obstructed with lavage ($n=10$), (3) obstructed without lavage ($n=10$), and (4) obstructed with lavage ($n=10$) All animals underwent initial laparotomy, and ligature obstruction of the rectum was performed in groups 3 and 4. Four days later intubation of the terminal ileum and distal colon was performed and 10^9 living ^{35}S-radiolabelled *Escherichia coli* inoculated into the colon of all animals. Groups 2 and 4 underwent colonic lavage with 0.9 per cent saline. Bacterial translocation was investigated with direct organ culture and liquid scintillation counting of organs for ^{35}S-radiolabelled *E. coli*

When group 4 was lavaged, *E coli* was cultured from regional nodes (100 per cent), liver (60 per cent), spleen (50 per cent), lung (40 per cent), kidney (40 per cent) and blood (80 per cent); this was significantly increased compared with groups 1, 2 or 3 ($P<0.05$, Fisher's exact test) Scintillation counts were significantly higher for all tissues and blood in group 4 ($P<0.05$, Wilcoxon rank sum test), confirming the colonic origin of translocating organisms These results suggest that peroperative lavage of the obstructed colon promotes significant bacterial translocation

Expression of p53 protein in colorectal cancer complicating ulcerative colitis

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Colorectal cancers frequently express mutations in *ras* and p53 Mutations in c-K-*ras* have been found less often in colorectal cancers arising in ulcerative colitis than in sporadic cases, suggesting that different genetic mutations underlie colitic cancers.

Overexpression of p53 in neoplastic cells can be detected immunohistochemically in 50–70 per cent of colorectal cancers and this correlates with the presence of point mutations in the p53 sporadic gene. This study examined the expression of p53 protein in a series of 20 colorectal cancers complicating ulcerative colitis using the polyclonal antibody Pab1801.

Overexpression of p53 determined by positive nuclear staining was observed in 11 cases (55 per cent) one showed strong staining that was focal, the other ten showed diffuse staining. Of these positive cases, four showed strong p53 immunoreactivity and seven weak staining No correlation was demonstrated between Dukes' classification or tumour grade and immunoreactivity.

These data indicate that the frequency of p53 mutation in cancers arising in ulcerative colitis is similar to that in sporadic colorectal cancers. This suggests that colitic cancers do not have a different genetic basis from sporadic colorectal cancers

Expression of c-*myc* in anal squamous neoplasia

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The presence and localization of the c-*myc* gene product p62 in anal squamous epithelium, normal and neoplastic, has been examined using immunohistochemical staining with the monoclonal antibody Myc I-6E10, in an attempt to assess c-*myc* as a marker of disease progression

Ten archival specimens of normal anal epithelium, ten of anal intraepithelial neoplasia (AIN) type III and 31 anal squamous cancers were examined There was a marked difference between the staining characteristics of the invasive tumours on one hand, and normal anal epithelium and AIN III on the other Intense diffuse mixed nuclear and cytoplasmic ($n=14$) and exclusively nuclear ($n=8$) staining in 22 (71 per cent) of invasive anal tumours was observed. All positively staining tumours were well differentiated histologically, whereas the negatively staining tumours (nine of 31, 29 per cent) were poorly differentiated ($n=7$) and moderately to well differentiated ($n=2$) In six positively staining tumour sections, adjacent areas of AIN III and non-dysplastic anal epithelium had staining characteristics similar to the invasive component. Staining in both normal anal epithelium (four of ten) and AIN III specimens obtained from patients without a history of invasive disease (eight of ten) was less intense, local in distribution and exclusively nuclear. No difference in staining characteristics could be detected in these two groups.

These results suggest that c-*myc* overexpression is implicated in the pathogenesis of anal squamous neoplasia and that immunohistochemical staining for c-*myc* protein may be helpful in identifying those AIN lesions most likely to progress to invasive tumours.

Humanized antibodies as mediators of colorectal cancer cell lysis

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The efficacy of monoclonal antibodies as antitumour agents is restricted by lack of specificity and antimurine antibody production The antitumour antibody-dependent cellular cytotoxicity (ADCC)-mediating capacity of the conventional monoclonal antibody 17-1A was compared with that of its chimerized analogue c17-1A and a new humanized chimeric antibody, cSF25, specific for colonic adenocarcinoma.

Peripheral blood mononuclear cells (PBMCs) were obtained from 20 patients with adenocarcinoma and 16 age- and sex-matched controls. All three antibodies were tested in an 18-h chromium-release ADCC assay against the colorectal cancer cell line LS180.

	No antibody	17-1A	c17-1A	cSF25
Controls	67·9(14·9)*	133·7(16·3)*	159·5(19)*	207·1(18·7)*†
Cancers	61·4(10·6)*	135·7(16·2)*	158·7(14·1)*	215·2(13·5)*†

Values are mean(s.e.m.) area under curve units calculated from standard effector:target ratios *$P<0{\cdot}0001$ *versus* no antibody, †$P<0{\cdot}0001$ *versus* 17-1A and c17-1A (paired *t* test)

These results demonstrate that PBMCs from patients with colorectal cancer mediate ADCC as effectively as those from healthy controls. However, both chimeric antibodies subserve ADCC more effectively than the conventional antibody, with cSF25 consistently producing the highest lysis This suggests that cSF25 is a potent mediator of ADCC *in vitro* and may represent a more effective antibody treatment for colorectal cancer as it is also less xenoimmunogenic.

Immunostimulation in patients receiving 5-fluorouracil with interferon alpha for advanced colorectal cancer

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Treatment with 5-fluorouracil (5-FU) plus interferon alpha (IFN-α) has proven efficacy in patients with advanced colorectal cancer, although the mechanism is unknown To determine whether this effect may have an immunological basis, cellular immunity was studied in 13 patients treated with 5FU–IFN compared with nine receiving standard treatment with 5-FU–leucovorin.

Cellular immune function was assessed before and throughout treatment by measurement of natural killer (NK) and lymphokine-activated killer (LAK) cell activity. NK cell number was measured by flow cytometry using the monoclonal antibody Leu11c (designated (CD16)

Treatment	Percentage ^{51}Cr release (ratio 50:1)		Peripheral lymphocytes (%)
	NK activity	LAK activity	
5-FU–IFN			
Pretreatment	40·1(3·6)	77·7(3·3)	11·1(1·6)
Day 5	45·0(3·8)*	78·2(2·0)	12·4(1·9)
Day 28	46·8(3·5)*	74·5(3·8)	11·5(1·2)
5-FU–leucovorin			
Pretreatment	50·1(4·2)	76·4(3·5)	11·6(1·9)
Day 5	42·8(4·7)†	56·0(6·3)†	11·5(2·1)
Day 28	42·9(5·0)*	68·6(3·5)*	10·8(1·8)

Values are mean(s.e.m.) *$P<0{\cdot}05$, †$P<0{\cdot}01$ *versus* pretreatment

NK and LAK activity was significantly reduced throughout treatment in patients receiving 5-FU–leucovorin By contrast, 5-FU–IFN augmented NK activity and there was no suppression of LAK activity. NK cell numbers remained unchanged in both groups, indicating an effect at the cellular level

In conclusion, cellular immunity is enhanced in patients receiving 5-FU–IFN-α for advanced colorectal cancer and this may contribute to its therapeutic efficacy.

Inhibition of colorectal cell proliferation by vitamin D analogues

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By reducing cell proliferation, vitamin D may protect against colorectal carcinoma, and the D_3 analogues calcipotriol and EB-109 lessen the risk of hypercalcaemia. The effects of these analogues on crypt cell production rate (CCPR) were investigated in patients with familial adenomatous polyposis (FAP) and on colorectal cancer cell growth in culture

Rectal biopsies were obtained from six patients with FAP and established in organ culture with or without calcipotriol (1×10^{-6} mol l^{-1}) After 15 h, vincristine (0·6 μg ml^{-1}) was added to induce metaphase arrest and CCPR was determined by linear regression analysis The cell lines HT-29 and CACO-2 (1×10^4 cells) were cultured for 21 days with or without calcipotriol or EB-109.

In patients with FAP, calcipotriol halved mean(s.e.m.) CCPR from 5·29(1·18) to 2·56(0·80) cells per crypt per h ($P<0{\cdot}05$). Each analogue produced a dose-dependent inhibition of cell growth in culture Calcipotriol reduced the number of CACO-2 cells by 58 per cent (at 10^{-10} mol l^{-1}), 89 per cent (10^{-9} mol l^{-1}) and 97 per cent (10^{-8} mol l^{-1}). EB-109 reduced CACO-2 cell number by 67 per cent (10^{-10} mol l^{-1}), 82 per cent (10^{-9} mol l^{-1}) and 92 per cent (10^{-8} mol l^{-1}), and HT-29 cell number by 72, 64 and 96 per cent. Each reduction was significant at $P<0{\cdot}001$.

These synthetic vitamin D_3 analogues inhibit colorectal epithelial cell proliferation in both FAP tissue and malignant cell lines

Improved survival of patients with colorectal cancer immunized with an anti-idiotypic antibody

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Internal image anti-idiotypic monoclonal antibodies should induce immune responses to tumour antigens by presentation of the antigen in a different environment. An anti-idiotypic monoclonal antibody to the tumour-associated antigen (TAA) gp72, 105AD7, has been used in a phase I study in 13 patients with advanced colorectal cancer. A control group of 16 patients concurrently recruited for the no-treatment arm of a phase III chemotherapy study with the same entry criteria were used for survival analyses.

A humoral immune response was not detected following treatment. Lymphocytes taken following 12 of 16 immunizations demonstrated a proliferative response on stimulation with gp72-bearing cells. Additionally, raised levels of circulating interleukin 2 were detected following 18 of 31 immunizations with 105AD7.

The median survival in the trial group was 12 months and in the control group 3 months. Comparison of survival using the Mantel–Haenszel test revealed significantly improved survival in the immunized group ($P<0{\cdot}001$). There was no toxicity attributable to the monoclonal antibody in this study.

105AD7 induced a cellular immune response directed against the TAA gp72 This immune response appears to confer a survival advantage, but this needs confirmation

New technique to measure mucosal metabolism and the characterization of regional metabolism in the large bowel

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To date, all studies on mucosal metabolic changes that accompany diseases such as ulcerative colitis, diversion colitis and pouchitis have been carried out on resection specimens. Thus it has been impossible to follow the progression of the disease and the possible effects of treatment. A technique has been developed whereby mucosal samples, of mass 5–15 mg, are incubated in cell culture media with radiolabelled glucose, glutamine or butyrate. After 2 h the amount of substrate oxidized is calculated. Analysis of variance of the intersample coefficient of variation was found to be 20, 28 and 16 per cent, respectively.

To assess regional variation in colonic metabolism, triplicate biopsies were taken from five regions of the large bowel of 13 patients undergoing normal colonoscopic examination and the amount of substrate oxidized was calculated.

	Substrate		
Region	Glucose*	Glutamine†	Butyrate‡
Ascending	491 (316–666)	2 929 (2 355–8 241)	30 595 (21 980–43 322)
Transverse	350 (197–560)	3 151 (2 223–11 027)	24 541 (16 464–44 750)
Descending	427 (292–634)	2 322 (1 339–7 208)	28 440 (20 067–32 474)
Sigmoid	454 (288–744)	1 850 (1 343–5 249)	24 114 (18 129–28 919)
Rectum	379 (252–604)	5 841 (2 883–8 717)	21 385 (14 072–30 642)

Values are median (95 per cent confidence interval) expressed in pmol per mg tissue per h. P not significant. *$H = 1·5$, †$H = 2·4$, ‡$H = 2·7$ (Kruskal–Wallis test)

This technique, which is simple and reproducible, allows for the first time study of human mucosa *in vivo* in health and disease. The results confirm that butyrate is the preferred fuel substrate, followed by glutamine and glucose. However, a decrease in glutamine and an increase in butyrate utilization from caecum to rectum, as has previously been suggested, could not be demonstrated.

Augmentation of vascular graft endothelialization using an angiogenic growth factor

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Pretreatment of prosthetic vascular grafts with endothelial cell (EC) mitogens may enhance their endothelialization. The effect of heparin-binding growth factor 1 (rHBGF-1) on synthetic graft healing was examined in this study. Modified fibrin glue (FG) containing this growth factor, heparin, fibrinogen and human thrombin (FG–HBGF-1) was pressure-perfused into expanded polytetrafluoroethylene (ePTFE) grafts (4 × 50 mm), coating both surfaces. Grafts were interposed into the aortoiliac position in 12 dogs. Control groups containing FG without rHBGF-1 or untreated grafts were similarly implanted. Tritiated thymidine ([^{3}H]TdR, 0·5 μCi kg^{-1}) was injected intramuscularly 10 h before explantation. Grafts were explanted at 7 and 28 days for light and electron microscopy, factor VIII immunohistochemistry, and autoradiography for EC proliferation. The retention of ^{125}I-labelled HBGF-1 showed a rapid initial loss with a mean(s.e.m.) of 13·4(6·9) per cent remaining at 1 week and only 3·8(1·1) per cent at 30 days. At 7 days 33 per cent of both the FG and FG–HBGF-1 groups demonstrated non-contiguous foci of ECs, whereas the surface of untreated grafts remained a fibrin coagulum. Every FG–HBGF-1 graft at 28 days showed extensive capillary ingrowth and confluent endothelialized luminal surfaces, not seen in control groups. Autoradiography revealed a significant increase ($P<0·05$) in [^{3}H]TdR incorporation into DNA of ECs in the FG–HBGF-1 grafts at 28 days *versus* all other groups.

It is concluded that rHBGF-1 affixation to ePTFE grafts promotes endothelialization via capillary ingrowth. This method may stimulate spontaneous endothelialization of grafts in humans.

Comparison of hand-held Doppler with duplex ultrasonography in venous disease

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Colour duplex scanning represents the current 'gold standard' in the non-invasive investigation of venous reflux but is not routinely available in most district general hospitals. Hand-held Doppler probes are widely available but not routinely used in venous assessment, despite reports of their accuracy.

The findings of two hand-held Doppler probes (a non-directional Huntleigh Mini Dopplex D500 and the directional Huntleigh Super Dopplex, both using 8-MHz probes) were compared with that of colour duplex scanning (Acuson 128, Acuson, Mountain View, California, USA) in a group of 50 patients referred for investigation of clinical venous disease. All limbs were examined for reflux at the saphenofemoral (SFJ) and saphenopopliteal (SPJ) junction and for deep venous insufficiency (DVI) using all three devices.

	SFJ reflux ($n=56$)		SPJ reflux ($n=27$)		DVI ($n=12$)	
Doppler	Sens.	Spec	Sens	Spec	Sens	Spec
Non-directional	89	84	78	92	24	97
Bidirectional	88	84	63	78	24	97

Values are percentages. Sens., sensitivity; Spec., specificity

The hand-held probes were useful at the groin and gave results comparable to those of duplex scanning. At the popliteal fossa, the results were less satisfactory, the major difficulty being the inability to distinguish between DVI and short saphenous insufficiency, resulting in a low sensitivity.

Capillary permeability in venous disease

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The capillaries in patients with chronic venous insufficiency are said to be more permeable than normal. The aim of this study was to determine the isovolumetric pressure (P_{vi}) and hydraulic conductance (K_f) of the calf capillaries in patients with lipodermatosclerosis (LDS).

Fifteen patients with LDS and 12 normal controls were studied. The rate of leg swelling following a thigh cuff inflated to 90 mmHg in steps of 10 mmHg, sustained for 5 min at each step, was measured using mercury in Silastic (Dow Corning) strain-gauge plethysmography. The slope of the last minute of each measurement was obtained and plotted against the cuff pressure. From this P_{vi} and K_f were calculated.

	P_{vi} (mmHg)	K_f (ml per min per 100 g per mmHg) × 10^{-3}
Controls ($n=12$)*	27·6 (18·6–32·7)	4·2 (3·2–5·4)
LDS ($n=15$)*	28·1 (15·6–30·7)	3·0 (2·5–4·0)
95% c.i. of difference	6·2 to −8·3	0·2 to −2·3

*Values are median (interquartile range). c.i., Confidence interval. Controls and LDS group were not significantly different (Mann–Whitney U test)

These results show that neither P_{vi} nor K_f is increased in the calf capillaries of patients with LDS compared with normal controls. This refutes the hypothesis that capillary permeability is increased in LDS.

Intimal proliferation follows damage to the vasa vasorum and is exacerbated by hypercholesterolaemia

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Atherosclerosis may be initiated by damage to the adventitial vasa vasorum. New Zealand White rabbits had the adventitia excised from the left carotid artery (study licensed under the Animals (Scientific Procedures) Act 1986). The right carotid arteries were mobilized to act as controls. Animals were fed either a normal or high-cholesterol diet for up to 6 weeks.

Computed image analysis calculated the mean(s.e.m.) intimal:medial ratio for control vessels as 0·038(0·002).

Adventitial excision induced the formation of an intimal proliferative lesion. With a normal diet, the lesion was maximal by day 14 (0·456(0·079), $n=8$; $P<0·01$, Student's paired t test), but thereafter showed regression to day 28 (0·080(0·025), $n=8$, $P=0·14$). Light and electron microscopy as well as immunocytochemistry indicated that this lesion was composed predominantly of smooth muscle cells.

With a high-cholesterol diet, the lesion was again maximal by day 14 (0·376(0·056), $n=8$, $P<0·01$), but regression was not as marked to day 42 (0·272(0·051), $n=8$, $P<0·01$). Cells were predominantly foam cell macrophages.

Adventitial excision promotes an intimal proliferative lesion, perhaps secondary to arterial wall ischaemia. Regression of mainly smooth muscle cell-based lesions may occur spontaneously, but in the presence of hypercholesterolaemia a macrophage-based lesion persists

Ultrasonographic differences between symptomatic and asymptomatic carotid plaques

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It has been shown that echolucent carotid plaques have increased lipid and cholesterol concentration, which makes them unstable and prone to ulceration and embolization. By contrast, echogenic plaques contain significantly more fibrin and collagen, and are less likely to embolize

The aim of this study was to test the hypothesis that, in the presence of more than 70 per cent stenosis in the carotid bulb, the ultrasonographic characteristics of plaques causing symptoms differ from those of asymptomatic plaques.

High-resolution B-mode ultrasonography was used to characterize plaques into four types: 1, echolucent plaques, 2, plaques of mixed echogenicity, 3, echogenic plaques; and 4, calcified plaques that could not be classified owing to heavy calcification and acoustic shadows

Thirty-two plaques in an equal number of consecutive symptomatic patients and 45 plaques in 33 consecutive asymptomatic subjects were characterized.

Plaque type	Symptomatic	Asymptomatic
1*	10	1
2†	20	32
3	0	10

*$P<0·002$ *versus* type 2, $P<0·0001$ *versus* type 3; †$P<0·02$ *versus* type 3 (χ^2 test)

Results support the hypothesis that echolucent plaques are more frequently associated with symptoms It is suggested, therefore, that this classification should be used in asymptomatic subjects prospectively followed up in natural history studies in an attempt to identify a high-risk group.

Vasodilatory capacity of the microcirculation in venous disease

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Impairment of vasodilatation in skin capillaries of patients with lipodermatosclerosis (LDS) in response to heating and ischaemia has been reported These stimuli produce vasodilatation through both direct action and local neural control of the capillaries The aim of this study was to determine the capacity of capillaries in liposclerotic skin to vasodilate in response to direct stimulation

Thirty patients with LDS and 20 normal controls were studied A Perspex chamber containing a laser Doppler probe was attached to the skin. The basal laser Doppler flux was recorded A 1 per cent solution of pilocarpine (a direct vasodilatory stimulus) was instilled into the chamber and electrophoresed into the skin using a 1-mA current and the peak laser Doppler flux recorded

Flux	LDS ($n=30$)*	Controls ($n=20$)*	95% c.i. of difference	P†
Basal	125 (72–277)	67 (60–82)	16 to 153	0·004
Peak	665 (382–1025)	765 (452–975)	−270 to 150	0·5

*Values are median (interquartile range) expressed in arbitrary units c.i., Confidence interval; †Mann–Whitney U test

The results show that the basal laser Doppler flux is higher in skin of patients with LDS than in normal skin. The capillaries in liposclerotic skin are able to achieve the same vasodilatation as normal skin in response to a direct stimulus This suggests that the previously reported impaired vasodilatation in response to heating and ischaemia may be caused by impairment in local neural control of vasodilatation

Comparative study of three primary dressings in the healing of chronic venous ulcers

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Many of the 100 000 patients in the UK with chronic venous ulceration remain unhealed indefinitely. Compression heals most venous ulcers but the role of different dressings remains debatable.

Consecutive patients with chronic venous ulcers (<10 cm^2) were randomized to treatment with either Granuflex E ($n=25$), Comfeel (Coloplast) ($n=25$) or non-adherent (NA) (Johnson and Johnson) ($n=25$), with weekly four-layer compression bandaging and ulcer area measurement by planimetry (ethics committee approval was obtained)

The initial mean(s.e.m.) ulcer area was 3·96(0·43) cm^2 for Granuflex E, 3·57(0·53) cm^2 for Comfeel and 4·8(0·63) cm^2 for NA (P not significant) By 6 weeks ulcer area had decreased by 2·98(0·44) cm^2 with Granuflex E, 2·09(0·51) cm^2 with Comfeel and 4·31(0·64) cm^2 with NA (P not significant) Median time to complete healing by the life-table method was achieved at 6·85 weeks for Granuflex E, 4·25 weeks for Comfeel and 6·17 weeks for NA (P not significant).

Eleven patients treated with Comfeel and seven with Granuflex E withdrew owing to skin maceration, compared with no withdrawals with NA ($P<0·05$, χ^2 test)

Expensive hydrocolloid dressings were no more effective than NA and were poorly tolerated by patients

Portal endotoxin and cytokine responses to abdominal aortic surgery

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Interleukin 6 (IL-6) is a major marker of tissue injury Surgery induces a systemic IL-6 response related to the magnitude of the operation An exaggerated IL-6 response is associated with the development of major complications following aortic aneurysm repair. Endotoxaemia is a potent stimulus for cytokine release and may occur during aortic surgery. The aim of this study was to examine whether the observed IL-6 response during abdominal aortic surgery is related to portal endotoxaemia.

Serial samples of inferior mesenteric and systemic venous blood were obtained before, during and after aortic cross-clamping in eight patients undergoing elective aortic aneurysm surgery.

Portal endotoxaemia was detected in only five of the eight patients during surgery and there was no correlation with the IL-6 response Both portal and systemic IL-6 levels rose during the course of surgery, but by the time of abdominal wound closure the mean portal IL-6 levels were eight times higher than the systemic IL-6 levels

	Systemic IL-6	Portal IL-6
Before cross-clamping	5 (0–12)	8 (0–17)
During cross-clamping (1)	10 (1–19)	50 (1–99)*
During cross-clamping (2)	17 (4–30)	97 (40–154)†
After cross-clamping	41 (22–60)	322 (75–569)†

Values are mean (95 per cent confidence interval) expressed in pg ml^{-1} *$P=0·02$; †$P<0·001$ (Mann–Whitney U test)

These results suggest that the portal circulation draining the colon is a major source of the previously observed systemic IL-6 response to aortic surgery The IL-6 response is not clearly related to portal endotoxaemia but may reflect occult cellular injury in the colon arising during surgery.

Surgical morbidity following primary systemic therapy for breast cancer: a randomized study

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Primary systemic treatment may influence surgical morbidity by interfering with host immunity and wound healing. The aim of this study was to assess the extent of complications associated with modified radical mastectomy following a period of systemic therapy

A group of 72 patients aged <70 years with operable primary breast cancer >4 cm in diameter were randomly allocated to undergo immediate mastectomy or to receive initial cytotoxic or endocrine treatment for 16 weeks, followed by mastectomy. Complications were recorded immediately after surgery and 2 weeks after discharge or until complete resolution, and were defined as minor (seroma, infection (oral antibiotics only), wound-edge necrosis (dressings only)) or major (infection (intravenous antibiotics or surgery), wound necrosis (excision required), loss of implant (any cause), systemic complications).

Thirty-five patients were treated by primary systemic therapy and 37 by primary surgery. There were no differences in age or initial stage of the disease between the groups. There were 12 minor and three major complications in the systemic therapy group and 14 minor and four major complications in the primary surgery group. The mean hospital stays were 9 and 12 days, respectively.

Compared with primary surgery, initial systemic treatment does not increase mastectomy-associated surgical morbidity.

Biologically active prolactin in patients with macroscopic breast cysts

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The role of prolactin in the development of macroscopic breast cysts is not clear. In breast cancer, prolactin measured by bioassay has been shown to reflect biological activity more accurately than when measured by radioimmunoassay. Administration of thyrotrophin-releasing hormone (TRH) stimulates prolactin release and peak response represents pituitary lactotroph activity.

Biologically active prolactin was measured using a rat Nb2 lymphoma cell microbioassay in the serum of 47 patients who presented with their first breast cyst and 27 age-matched controls. In 28 of the patients with breast cysts and ten controls, peak responses to TRH were also measured.

Subjects	Serum prolactin ($ng\,ml^{-1}$) Basal	 Peak
Breast cysts	6·0(0·5)*	144·9(12·0)*
Controls	4·2(0·7)	95·3(17·0)

Values are mean(s.e.m.). $^*P<0{\cdot}05$ (unpaired t test)

Basal and peak biologically active prolactin levels were significantly raised in patients with breast cysts compared with controls. These findings suggest an active role for prolactin in the development of breast cysts and a possible role for prolactin suppression with bromocriptine to reduce recurrent breast cyst formation. Further investigation should be undertaken by placebo-controlled trial.

Stereotactic fine-needle aspiration cytology: a prospective study

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Stereotactic localization and fine-needle aspiration have not gained widespread acceptance in the management of non-palpable mammographic abnormalities. In this prospective study, stereotactic guided cytology was performed with immediate reporting before biopsy in a consecutive series of 166 patients with screen-detected non-palpable abnormalities.

Specimens were obtained by multiple passes through the abnormality with a 22-G Franzen needle and after conventional staining the cytological diagnosis was made as (I) inadequate, (II) benign, (III) atypical, (IV) suspicious or (V) malignant. After definitive surgery all tumours were staged according to the Union Internacional Contra la Cancrum classification by an independent pathologist.

Of 62 patients with invasive malignancy, 58 (94 per cent) were correctly diagnosed cytologically. Only one of a further ten patients with carcinoma *in situ* had positive cytological results. Four patients with benign disease had atypical cytology but there were no false-positive patients in this series.

As 45 of the 62 patients with invasive carcinoma had stage I disease, a positive cytological diagnosis allows potentially curative wide local excision in a majority of screen-detected malignancies. Although open biopsy is still necessary in patients with negative cytological findings, this has important implications for the health service.

Prediction of response to tamoxifen in elderly women with breast cancer

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In view of the known effect of tamoxifen in prolonging life when given with other treatments, the recent trend has been to treat elderly women with tamoxifen first. However, the time needed to assess response is considerable and complicated by the number of patients with static disease who subsequently relapse.

This study was undertaken to define parameters that would predict which patients would have a worthwhile response, as defined by control of disease at 2 years from the start of treatment.

Criteria examined were: (1) initial response according to the Union International Contra la Cancrum (UICC) criteria (complete or partial) at 3 and 6 months, (2) analysis of a regression line drawn through sequential calliper measurements of tumour size during the first 12 weeks of treatment; and (3) immunocytochemical staining (oestrogen receptor immunocytochemical assay (ER-ICA)) of fine-needle aspirates for ER.

Predictive technique	No. of patients	Predicted response	Sensitivity (%)	Predicted failure	Specificity (%)
UICC					
3-month	59	7 of 32	22	12 of 27	44
6-month	59	16 of 32	50	18 of 27	67
12-week measurements	59	21 of 32	66	12 of 27	44
ER-ICA*	47	26 of 27	96	12 of 20	60

* < 20 or ≥ 20 per cent of cells stained

The results indicate that none of the clinical methods of assessment predicts response as well as the ER-ICA (sensitivity 96 per cent).

Safety of immediate postmastectomy reconstruction in the long term

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The role of immediate postmastectomy reconstruction (IPR) has remained contentious. One concern has been the possibility that a more major operation may have an adverse effect on host resistance and enhance tumour dissemination.

To assess any detrimental effects of IPR, a prospective case–control study of 81 patients was carried out. Each patient had been matched for tumour size, pathological lymph node status, age and procedure with a control patient who underwent mastectomy alone.

The reconstructive procedure used varied according to the particular problems posed by the patient and the preference of the surgeon, eight patients had simple subpectoral insertion of prosthesis, seven had subpectoral prosthesis covered by a thoracoepigastric flap, 35 had a rectus abdominis myocutaneous flap and 33 had a latissimus dorsi flap reconstruction.

After a complete follow-up of 10 years the local recurrence rate has been 11 per cent ($n=9$) and 14 per cent ($n=11$), the systemic recurrence rate 38 per cent ($n=31$) and 36 per cent ($n=29$), and relative survival 62 per cent ($n=50$) and 64 per cent ($n=52$) in the IPR and control patients respectively. No difference in outcome has been found in the two groups using the method of sequential analysis. These data support the view that IPR does not have any long-term detrimental effects.

Importance of orientated specimen radiology in stereotactic wide local excision of impalpable breast cancers as an aid to complete excision

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Wide local excision (WLE) of impalpable breast cancers can result in fewer than half of the lesions being adequately excised.

Eighty patients with impalpable localized lesions underwent hooked-wire guided WLE during a 2-year period because of malignant (49) or suspicious (23) stereotactic or ultrasonographically guided fine-needle aspiration cytology or where malignant mammographic characteristics were present in the presence of acellular (seven) or benign (one) cytology. WLE included tissue anteriorly up to subcutaneous fat and posteriorly down to the pectoral fascia. After excision the specimen was orientated (one Ligaclip (Ethicon) anteriorly, two Ligaclips medially, three Ligaclips inferiorly) and radiographed with the anterior surface upwards. If on the specimen radiograph the visible lesion approached any excision margin, further tissue was excised and orientated.

In all, 77 of 80 lesions were malignant (20 *in situ*, 57 invasive breast cancer). Clear histological margins were obtained on the first excision specimen in 52 of 77 cancers (68 per cent). Further tissue was excised in 22 patients and this significantly increased complete excision to 86 per cent (66 patients) ($P < 0·01$). This complete excision rate was almost identical to that obtained after WLE of palpable breast cancers, 304 of 360 WLEs (84 per cent).

Orientated specimen radiology improves the complete excision rate of impalpable localized malignant mammographic lesions and this should now be routine practice.

Abnormal colorectal cancer genes also occur in patients with breast cancer

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It is now well established that defects in tumour suppressor genes allow human cancers to develop. This study examined whether abnormalities of two such genes important in colorectal cancer, the adenomatous polyposis coli gene *apc* and the deleted in colon cancer gene)*DCC*), also occur in breast cancer.

Constitutional lymphocyte DNA and tumour DNA, RNA and protein were extracted from 20 patients with breast cancer. Southern blots were examined for allele loss in the tumour DNA at the *apc* and *DCC* loci using eight gene probes. *DCC* gene expression in the tumours was determined on Northern blots of RNA and, using a monoclonal *DCC* antibody for the protein, on Western blots.

At the *apc* locus, results from 15 of 20 patients were informative and three of 15 had allele loss in the tumour. For *DCC*, results from 13 of 20 patients were informative and five of 13 tumours had allele loss. All five expressed abnormal *DCC* RNA species, but no *DCC* protein was detectable in these tumours. As the *DCC* gene encodes a cell adhesion molecule, loss of *DCC* expression may be important in breast carcinogenesis.

Abnormalities in the *apc* and *DCC* genes occur in breast, as in colorectal, cancer.

Somatostatin treatment for hyperparathyroidism

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Primary hyperparathyroidism is one of the commonest syndromes of endocrine overactivity. No satisfactory medical therapy exists and calcitonin and diphosphonates do not give good long-term control of disease. This work examines the efficacy of a somatostatin analogue in the management of hyperparathyroidism.

Ten patients were admitted before parathyroid surgery. Each was treated for 6 days with subcutaneous Sandostatin (Sandoz) at a dose of 100 μg twice daily. Fasting blood samples were taken for serum calcium and parathyroid hormone (PTH) determination before and after treatment, and 24-h urinary calcium excretion was measured before and after treatment. Eight patients have so far had successful surgical resection of parathyroid adenomas.

	Serum Ca (mmol l^{-1})	24-h total Ca (mmol per sample)	24-h Ca creatinine ratio	PTH (pmol l^{-1})
Pretreatment	2·76 (2·57–3·27)	5·50 (1·8–13·5)	0·71 (0·24–1·91)	10·5 (4·2–27·9)
Post-treatment	2·66 (2·37–3·15)	3·80 (0·7–13·4)*	0·54 (0·06–1·19)*	13·6 (5·9–17·4)

Values are median (range). $^*P < 0·05$ (paired *t* test)

Sandostatin may provide therapy for patients with hyperparathyroidism who have undergone unsuccessful neck exploration or who are unfit for surgery. It may ameliorate hypercalciuria, reduce stone formation and allow correlation of restoration of biochemical normality with symptom control.

Variation in oestrogen and progesterone receptor status in breast cancers during the menstrual cycle

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Recent claims have been made that the time of operation in relation to the menstrual cycle influences prognosis in breast cancer. The aim of this study was to investigate the effect of the menstrual cycle on oestrogen receptor (ER) and progesterone receptor (PR) status in primary breast cancer.

Patients were studied in whom the exact date of the last menstrual period before surgery was known. Of these 161 patients, ER status was available for 129, and PR status for 81.

A larger percentage of ER-negative tumours was observed during the mid-cycle through the early luteal phase (days 14–23) compared with the remaining days (0–13, 24–32): ER-negative 71 *versus* 38 per cent ($\chi^2 = 12·5$, 1 d.f., $P < 0·001$).

It is suggested that the excess ER-negative tumours during days 14–23 are positive at other times during the cycle (i.e. they are false-negative on days 14–23).

Both ER-negative subgroups (days 14–23 *versus* others) were compared with respect to overall survival and a significant difference was found, favouring the group from days 14–23. This supports the above suggestion.

These findings suggest that apparent ER status does vary during the menstrual cycle and that sampling for ER on days 14–23 is less accurate because of false-negative results.

Dual immunocytochemical staining of receptors for oestrogen and epidermal growth factor in human breast cancer

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Recent studies have demonstrated a consistent inverse relationship between the oestrogen receptor (ER) and the epidermal growth factor receptor (EGFR) in human breast cancer. Serial cross-section studies using immunocytochemical assays (ICAs) have suggested that separate populations of ER-positive–EGFR-negative and ER-negative–EGFR-positive cancer cells exist.

Using the cell culture lines MCF-7 and A431, a dual ICA has been developed that is able to stain for both ER and EGFR using two sequential indirect immunoperoxidase systems on a single 5-μm frozen section sample. After refinement, this technique was applied to 22 samples of human breast cancer deemed by single ER-ICA and EGFR-ICA to be positive for both ER and EGFR.

There was no significant difference in receptor positivity between the single or dual ICAs for ER ($P = 0·39$) or EGFR ($P = 0·48$) (Student's *t* test). Individual cancer cells exhibited three staining patterns: nuclear staining alone (ER-positive–EGFR-negative), membrane–cytoplasmic staining alone (ER-negative–EGFR-positive) or no staining (ER-negative–EGFR-negative). No cancer cells exhibited both nuclear and membrane–cytoplasmic staining.

This is the first description of a simultaneous dual ICA for ER and EGFR in human breast cancer. The results suggest that ER and EGFR expression is mutually exclusive within an individual cancer cell, raising the issue of a clonal distribution within breast cancer.

Significance of pS2 immunoreactivity in breast cancer

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Immunohistochemical (pS2) assay provides predictive information on response to endocrine therapy in primary breast tumours; however, the significance of the patterns of immunoreactivity is obscure, prompting this study of 194 carcinomas, utilizing a monoclonal antibody to pS2 protein, on formalin-fixed paraffin-embedded tissues.

Staining was observed in 167 cases (86 per cent), 90 of which (54 per cent) had more than 50 per cent positive cells. Reactivity was either granular cytoplasmic (cy) or peripheral/luminal (p/l) in distribution and was seen in 123 (74 per cent), and 100 (60 per cent) cases, respectively, with the former pattern having 58 per cent of cases with more than 50 per cent positive cells and the latter having 46 per cent. Both patterns of reactivity correlated with grade of differentiation (cy, $P < 0·05$, p/l, $P < 0·01$), but only cytoplasmic reactivity was associated with menopausal status ($P < 0·05$) and only peripheral reactivity with oestrogen receptor (ER) status ($P<0{\cdot}05$) Neither pattern was associated with progesterone receptor (PR) status, nor with combined ER–PR status. Lymph node status, relapse-free survival and overall survival also had no correlations Both patterns of reactivity, independently, were significantly associated with prediction of response to endocrine therapy on relapse ($P<0{\cdot}001$), however, peripheral reactivity appears to be more specific. Overall, pS2 reactivity can identify which patients in the subgroups of moderate and poorly differentiated tumours are not likely to benefit from endocrine therapy ($P<0{\cdot}001$).

Role of basic fibroblast growth factor and its receptor in human breast cancer

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Basic fibroblast growth factor (bFGF) is a pluripotential growth factor for mesenchymal cells, although it is not clear whether it is mitogenic for epithelial cells

It was attempted to determine whether (1) bFGF can stimulate breast cancer cell lines via a functional specific receptor, and (2) it is present in human breast cancers, using a streptavidin–biotin complex immunoperoxidase assay utilizing antibody to recombinant bFGF and *in situ* hybridization for bFGF messenger RNA.

Growth of the T47D (but not MCF7) cancer cell line was stimulated by bFGF alone. A novel mitotoxin, bFGF–saporin (a conjugate of bFGF and the ribosome-inactivating protein saporin), caused cell killing at concentrations of 1 and 10 nmol l^{-1} (34 and 8 per cent control cell amounts seen at 7 days) whereas saporin and unconjugated bFGF together at the same concentrations stimulated growth (182 and 134 per cent, respectively)

Forty-four (39 per cent) of 112 early breast cancers had positive immunoperoxidase staining for bFGF and 11 (10 per cent) equivocal staining. *In situ* hybridization confirmed the presence of messenger RNA for bFGF and its receptor (bFGF receptor flag, flg) in epithelial cancer cells Staining was not related to node status, tumour size, grade, histological type or oestrogen receptor status

Breast cancers produce bFGF and express specific receptors for bFGF. The bFGF receptor may be a potential target for therapeutic manipulation.

Effect of tamoxifen on concentrations of insulin-like growth factor 1 and insulin-like growth factor-binding protein 1 in women with advanced breast cancer

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The antioestrogen tamoxifen is widely used in the treatment of breast cancer and acts mainly by blocking the interaction of oestradiol with its receptor As there is evidence that tamoxifen may also act to alter the production of stimulatory or inhibitory growth factors, the effect of treatment with tamoxifen (100 mg/day for 2 weeks) on plasma insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 1 (IGFBP-1) concentrations was examined. The effects of other endocrine agents, medroxyprogesterone acetate (MPA) (500 mg/day for 2 weeks) and 4-hydroxyandrostenedione (4-OHA) (2 x 500 mg, intramuscularly) were also examined

After treatment with tamoxifen, the mean(s d) plasma IGF-1 concentrations decreased (80(18) *versus* 67(17) ng ml^{-1}, $n=10$, $P<0{\cdot}05$) whereas IGFBP-1 levels increased (35(30) *versus* 67(45) ng ml^{-1}, $P<0{\cdot}001$). In contrast, treatment with MPA increased IGF-1 levels (62(37) *versus* 129(87) ng ml^{-1}, $n=7$, $P<0{\cdot}02$) but decreased IGFBP-1 concentrations (38(31) *versus* 9·9(4·0) ng ml^{-1}, $P<0{\cdot}05$). Treatment with 4-OHA did not result in an overall change in concentrations of IGF-1 or IGFBP-1

From this study it is concluded that, in addition to its specific receptor-mediated effects, tamoxifen acts to reduce IGF-1 and increase IGFBP-1 concentrations The combination of a decrease in IGF-1 and increase in IGFBP-1, which antagonizes the action of IGF-1, may contribute to the beneficial effects associated with the use of tamoxifen

Natural killer cell cytotoxicity in patients with breast cancer receiving neoadjuvant chemotherapy in combination with L-arginine

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Cytotoxic drug regimens are known to inhibit anticancer host defences, an effect that may persist for up to 6 months Cytotoxic regimens that do not suppress host antitumour defences are currently being evaluated

L-Arginine in women with locally advanced breast cancer ($n=16$) increased natural killer (NK) and lymphokine-activated killer (LAK) cell cytotoxicity (mean percentage increase 81 and 107 per cent respectively, $P<0{\cdot}001$).

Patients then had four cycles of CHOP (cyclophosphamide (1 g m^{-2}), vincristine (1·5 g m^{-2}), Adriamycin (50 mg m^{-2}) and prednisolone (40 mg)) neoadjuvant chemotherapy orally for 5 days at 3-week intervals Arginine (30 g/day for 3 days) was given before each cycle of chemotherapy NK cell cytotoxicity was measured on day 1 of each cycle (before starting arginine), on day 4 (following arginine, and before CHOP), on day 9, on day 14, and subsequently on day 21 (day 1 of next cycle)

Mean NK cell cytotoxicity was low on day 14 (maximum myelosuppression) of each cycle, but by day 1 of cycles 2, 3 and 4 tended to return to the mean pretreatment value ($n=8$, 7 and 6) In each cycle, there was a significant increase in NK and LAK cell cytotoxicity following 3 days of oral arginine

	Cycle		
Cytotoxicity	2	3	4
NK ($n=6$)	178*	129†	54‡
LAK ($n=4$)	104§	126#	57¶

Values are mean percentage increase *$P=0{\cdot}013$; †$P=0{\cdot}04$, ‡$P=0{\cdot}004$, §$P=0{\cdot}01$, #$P=0{\cdot}011$, ¶$P=0{\cdot}006$ (paired *t* test, log-transformed data)

In summary, arginine is able to stimulate NK and LAK cell cytotoxicity repeatedly in patients who are receiving chemotherapy. Arginine, therefore, reverses the immunosuppressive effects of this cytotoxic therapy.

Criteria for selection for breast conservation of patients with primary operable breast cancer

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Between November 1979 and December 1986, 263 women were treated for primary breast cancer by local excision and external beam radiotherapy Local recurrence within the treated breast has occurred in 70 women. In 18 recurrence was gross and uncontrollable, in 14 of these, recurrence occurred by 24 months.

A retrospective analysis of clinicopathological features showed patient age, vascular invasion, tumour size and node status to be predictive of breast cancer recurrence

Breast conservation is now not advised, therefore, if the tumour is larger than 3 cm on clinical or mammographic measurement or if there is mammographic evidence of extensive or multifocal disease In the presence of vascular invasion, only women aged over 50 years or those with tumours measuring < 1 cm are considered suitable to continue with this treatment Re-excision is advised if the excision margin is < 5 mm

In a prospective study, 309 women have been managed according to these new criteria, with a median follow-up of 24 (range 3–50) months. Five women have developed ipsilateral breast recurrence and in none was this of the uncontrolled aggressive type

It is concluded that, by using the above criteria, the great majority of local recurrences and particularly of uncontrolled recurrences of breast cancer have been avoided

Changes in tumour markers during primary systemic treatment for breast cancer

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The role of tumour marker assays in the assessment of primary breast cancer remains uncertain The aim of this study was to assess the value of breast cancer-specific tumour markers CA15-3 and HMFG2 in detecting response to primary systemic treatment

Thirty-one patients with operable primary tumours >4 cm in diameter were given 12–16 weeks of systemic therapy followed by mastectomy. Response was determined using weekly ultrasonographic examination. Serum was sampled before the start and at monthly intervals during treatment. Samples were obtained before and after mastectomy from 41 patients They were stored at −20°C and assayed for CA15-3 and HMFG2 simultaneously

HMFG2 levels showed an overall reduction in 22 responding patients ($P = 0\cdot027$, Wilcoxon signed rank test). No change was observed in non-responders. CA15-3 levels did not change with response. CA15-3 and HMFG2 levels fell significantly following mastectomy ($P = 0\cdot003$ and $P = 0\cdot005$ respectively). Sequential HMFG2 levels fell in 11 of 22 responders and one of nine non-responders (accuracy 64 per cent) CA15-3 fell in seven of 22 responders and one of nine non-responders (accuracy 52 per cent)

CA15-3 and HMFG2 levels reflect changes in tumour bulk in large operable primary breast cancers. They are of little value in monitoring individual primary tumours

Paracrine control of aromatase activity by interleukin 6 in breast cancer cells

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Many breast tumours are hormone dependent, requiring oestrogen to support their growth The enzyme required for oestrogen synthesis, aromatase, is present in normal and malignant breast tissues, and factors produced by breast tumours may stimulate its activity To investigate such a possibility, conditioned medium (CM) was collected from cultured tumour-derived fibroblasts and the ability of CM to stimulate aromatase activity in breast cells was examined. For this, fibroblasts were cultured from normal and malignant breast tissues and aromatase activity assayed in the presence of dexamethasone (100 nmol l^{-1}) using a tritiated water release technique In control cells, aromatase activity was <5 fmol per 4 h per 10^6 cells Treatment with CM (50 per cent (v/v)) significantly stimulated activity, up to 300 fmol per 4 h per 10^6 cells. Column chromatographic and immunological techniques have identified the cytokine interleukin 6 (IL-6) as the aromatase-stimulatory factor present in CM Using a tissue explant system, mean(s.e m.) production of IL-6 by breast tumour tissue (232(130) ng g^{-1}) has been found to be significantly higher ($P < 0\cdot001$) than that by normal tissue explants (54(50) ng g^{-1}) It is concluded that IL-6 has a major role in regulating aromatase activity in breast tissues and that its production by breast tumours may influence aromatase activity in tissues adjacent to the tumour.

Different regulatory effects of inhibitory monocyte cytokines on monocyte function

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The monocyte/macrophage is important in tumour oncology, but overactivation *in vivo* may be harmful in patients with sepsis or trauma Whereas more and more monocyte primers are being identified, the inhibitory monocyte cytokines are less studied. Cytokines that may possess inhibitory effects on monocyte function have been investigated.

Human peripheral blood monocytes were used in this study with the following cytokines interleukins IL-4 and IL-10, transforming growth factor beta (TGF-β) and monocyte-deactivating factor (MDF) derived from P815 malignant cells

The following monocyte functions were studied. tumour necrosis factor (TNF) production stimulated by lipopolysaccharide, hexosaminidase (Hex) secretion stimulated by (1) phorbol myristate acetate (PMA) and (2) opsonized zymozan, formazan production from nitroblue tetrazolium (NBT), and phagocytosis

Monocyte function	Nil (control)	IL-4	IL-10	TGF-β	MDF
TNF (units ml^{-1})	119·2(28·0)	90·4(24·5)	60·5(27·3)*	31·7(7·2)*	6·0(2·0)*
Hex (PMA) (units l^{-1})	44·4(5·8)	38·4(4·7)*	35·4(4·9)*	43·4(6·5)	45·8(6·9)
NBT ($\mu\text{g ml}^{-1}$)	31·3(1·9)	25·8(3·1)	28·6(1·9)	24·7(0·7)*	25·1(2·8)

Values are mean(s.e m.) *$P < 0\cdot05$ *versus* control (Student's *t* test)

None of the cytokines inhibited opsonized zymozan-stimulated Hex secretion nor phagocytosis by monocytes.

It is concluded that inhibitory monocyte cytokines regulate monocyte function in different ways. IL-10 and TGF-β inhibit a wide range of activities, but tumour-derived MDF inhibits only monocyte TNF production

Tumour lysis by bispecific antibody is directly related to tumour expression of a target antigen

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Bispecific antibodies (BAbs) direct cytotoxic T lymphocytes (CTLs) to lyse tumour targets based on recognition of specific surface antigens, but tumour metastases may differ from the parent tumour in antigen expression BAb treatment may therefore result in selective growth of tumour clones that do not express the target antigen. This study assessed tumour lysis by cultured murine CTLs, with or without BAb, of a range of human and murine melanomas with varying expression of the target antigen p97 and of major histocompatibility complex (MHC) class I and II antigens

Three human melanoma cell lines (LR, JH and FT) and two murine melanomas (K1735 and CL62) were used as tumour targets in 4-h chromium release assays Effector cells were cultured murine CTLs with or without BAb.

Melanoma	MHC class	p97	CTLs*	CTLs plus BAb*	P†
CL 62	I	+	1(0·1)	53(11)	<0·01
FT	I, II	−	2·5(0·7)	2·5(0·7)	n.s
LR	—	+	1(1)	29(10)	<0·01
JH	I	+	0·3(1)	17(4)	<0·01
K1735	I	−	2(0·1)	2(0·1)	n s.

*Values are mean(s d.) expressed in lytic units. †Student's *t* test, n s., not significant

Tumour lysis by CTLs plus BAb is directly related to surface expression of target antigen, but is not affected by class I or II MHC expression

Gamma linolenic acid inhibits cell motility induced by hepatocyte growth factor/scatter factor

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Hepatocyte growth factor/scatter factor (HGF/SF) is a recently identified cytokine that increases the motility of some malignant cells and induces DNA synthesis in primary cultures of hepatocytes The regulation by gamma linolenic acid (GLA) of the HGF/SF-induced motility of colonic cancer cells has been investigated.

The human colonic cancer cell line HT115 was used. Cell motility was measured using cell dissociation from carrier beads and a colony scatter assay HGF/SF increased cell dissociation from carrier beads in a dose-dependent manner (range 0·1–10 ng ml^{-1}, $r = 0\cdot99$, $P < 0\cdot001$) When cells were cocultured with HGF (4·0 ng ml^{-1}) and GLA, the dissociation was reduced.

		GLA concentration ($\mu\text{mol l}^{-1}$)			
	Medium	1	10	50	100
Control	39·1(7·1)	19·6(1·6)*	12·3(1·9)*	12·7(2·8)*	21·5(3·1)*
HGF	123·3(13·3)†	98·0(11·8)	73·8(8·2)*	53·1(7·3)*	38·7(6·2)*

Values are mean(s e.m.) number of cells released from beads and counted (per high-power field) on the culture well floor. *$P < 0\cdot05$ *versus* cells with medium only, †$P < 0\cdot05$ *versus* control (Student's *t* test)

GLA in a similar concentration range also reduced colony scattering induced by HGF/SF.

It is concluded that whereas HGF/SF greatly increases the motility of colonic cancer cells, the n-6 fatty acid GLA greatly reduces the motility induced by this factor This may provide the background for the therapeutic use of GLA in patients with cancer.

Vasoactive agents do not increase blood flow to liver metastases but endothelin does produce a rise in tumour:normal blood flow ratio

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Angiotensin has been shown to increase the uptake of microspheres into liver metastases. However, the extent and duration of these changes and the potential of other vasoactive agents has not been fully established. Hepatic parenchymal and tumour perfusion has been measured in 38 Chester Beatty Hooded rats bearing HSN hepatic tumours before and during a 30-min hepatic artery infusion of vasoconstrictor (angiotensin, endothelin, or vasopressin) or a potent vasodilator (calcitonin gene-related peptide (CGRP)). Systemically infused endothelin was also assessed. Perfusion was continuously measured by laser Doppler flowmetry.

	n	Perfusion change (%)*		Proportion with flow recovery to baseline (%)	TNR change (%)	Significance of TNR change (*P*)
		Tumour	Liver			
Hepatic artery						
Angiotensin	9	−15	−5·1	55	−3·2	n.s.
Endothelin	8	−23·1	−34·8	0	29·6	<0·01
Vasopressin	7	−27·5	−24·6	100	−5·3	n.s.
CGRP	7	−14	−13·8	57	5·9	n.s.
Systemic						
Endothelin	7	−11·5	−23·7	14	28·2	<0·01

*Values are changes in mean perfusion between baseline and infusion periods. TNR, tumour normal blood flow ratio, n.s., not significant

No agent increased tumour perfusion. Only endothelin produced a sustained rise in TNR. Angiotensin, CGRP and vasopressin showed little potential to increase TNR when given by regional infusion. TNR can be improved by regional or systemically administered endothelin but increased cytotoxic drug uptake has yet to be demonstrated.

Clinical responses to tumour-activated killer cell immunotherapy in patients with liver metastases

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Recent trials have confirmed the clinical potential of adoptive immunotherapy. However, the immunotherapy, using tumour-infiltrating lymphocytes (TILs) remains restricted to malignant melanomas and is complicated by severe side-effects related to the concurrent use of interleukin 2 (IL-2). Tumour-activated killer (TAK) lymphocytes have been shown to localize, *in vivo*, metastatic sites from a variety of tumours, including pancreatic, colorectal and ovarian. TAK cells are easy to produce and do not require maintenance with IL-2 *in vivo*.

This study reports the outcome of ten patients with hepatic metastases who have received 12 months of TAK cell immunotherapy. All patients showed tumour progression on chemotherapy. The patients received 1–5 × 10^8 TAK cells, given as a bolus intravenous injection at monthly intervals. Computed tomography was performed at the start of therapy and at 3-month intervals thereafter. Four patients responded, with the reduction of metastases ranging from 80 to 30 per cent, two patients remained static and four showed tumour progression.

This study confirms the ease of production of TAK cells, and patient tolerance of TAK cell immunotherapy, with a 40 per cent response rate in this small group.

Role of the immune system in the response to chemoembolization of liver cancer

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Chemoembolization of liver cancer is a useful therapeutic option, particularly in the case of irresectable disease. It is not clear, however, whether its antitumour action is due solely to ischaemic necrosis.

This study investigated whether chemoembolization could increase host tumour necrosis factor (TNF) production, and whether this was associated with a tumour response to therapy. Chemoembolization with Lipiodol (May and Baker) and doxorubicin was performed ($n = 12$) by selective arterial cannulation using the Seldinger technique. Peripheral blood mononuclear cells were cultured on day 0 (pre-embolization), day 1 and day 4, and lipopolysaccharide-induced TNF production determined (L929 bioassay).

Median TNF production was unchanged 1 day after the procedure (day 0, 677 pg ml^{-1}, day 1, 820 pg ml^{-1}), but was raised on day 4 (2545 pg ml^{-1}, $P = 0{\cdot}01$, paired Wilcoxon test). Ten patients were followed up for >2 (median 3) months. There was one partial response (>50 per cent reduction in tumour size) and three minor responses (sustained 50 per cent reduction of tumour markers, or >20 per cent reduction in tumour size). Median day 4 TNF production was higher in patients who responded (5005 pg ml^{-1}) than in those who did not (1082 pg ml^{-1}, $P = 0{\cdot}04$, Mann–Whitney *U* test).

Chemoembolization increases endogenous TNF production, and this may be associated with a greater likelihood of a tumour response. Therapeutic augmentation of TNF production may well improve treatment efficacy.

Inhibitors of growth factors in the therapy of hormone-resistant prostate carcinoma

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Prostate cancer cells no longer responsive to conventional hormonal manipulation provide their own fuel in the form of autocrine and paracrine growth factors that stimulate tumour growth in the absence of circulating androgens. Tumour progression may be influenced by growth factor regulators. This study evaluated the impact of the somatostatin analogue SMS 201-995 and of suramin, drugs capable of blocking the activity of basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), on the growth *in vitro* of androgen-independent cancer of the prostate cell line PC3.

Tumour cells were adapted to growth in serum-free media containing RPMI 1640–ITS (insulin, transferrin, selenous acid). Cells were exposed to concentrations of SMS 201-995 (range 0–20 μg ml^{-1}) or suramin (range 0–810 μg ml^{-1}). Cell counts were carried out on days 0, 2, 4 and 6. Compared with the suramin-free control, suramin produced inhibition of cell growth in a dose-dependent manner up to a maximum concentration of 270 μg ml^{-1}. At 270 μg ml^{-1} suramin produced 49 per cent inhibition of growth of cell line PC3 on day 6. SMS 201-995 produced inhibition of cell growth in a dose-dependent manner in PC3. It produced 51 per cent inhibition at 20 μg ml^{-1} SMS 201-995 on PC3.

Suramin and SMS 201-995 have an inhibitory role in the growth of hormone-resistant cancer of the prostate in doses that are achievable *in vivo*. This finding opens new avenues of therapy.

Long-term follow-up related to epidermal growth factor receptor status in bladder cancer

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Overexpression of epidermal growth factor receptor (EGFR) occurs in certain human tumours and can be of prognostic significance. From 1984 to 1990, fresh tumour biopsies from 212 patients were stained for EGFR using an immunohistochemical technique. A total of 99 patients had tumours invading bladder muscle (T_{2-4}) and 113 had pT_a or pT_1 disease.

Overall, 88 tumours (42 per cent) were EGFR positive. A strong association was confirmed between EGFR positivity and high tumour stage ($\chi^2 = 51{\cdot}4$, $P < 0{\cdot}0001$). In all, 82 patients (39 per cent) died during the study period; in 61 (29 per cent) of the total 212 patients the deaths were from bladder cancer. For pT_a tumours, the recurrence rate (mean(s.e.m.) per 100 patient-months) was significantly higher for EGFR-positive tumours (18·1(12·6)) than those that were EGFR negative (7·6(8·6)) ($P < 0{\cdot}05$, Mann–Whitney *U* test). Stage progression occurred in 19 of 113 pT_a or pT_1 tumours and was more likely in EGFR-positive tumours (ten of 23) than in EGFR-negative lesions (nine of 90) ($\chi^2 = 14{\cdot}7$, $P < 0{\cdot}001$). Using Cox's multiple regression analysis, EGFR positivity was associated with death from bladder cancer ($P = 0{\cdot}004$) and with tumour stage progression in non-invasive cancers ($P = 0{\cdot}0004$).

These long-term follow-up data support the initial suggestion that EGFR positivity is associated with a poor clinical outcome.

Evaluation of interleukin 2 nephrotoxicity in humans: lithium clearance measurements and enzymuria

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Renal dysfunction commonly occurs in patients undergoing recombinant interleukin 2 (rIL-2) therapy, as assessed by elevations of serum urea and creatinine. However, a more sensitive assessment of the effect of rIL-2 on the different parts of the nephron can be obtained using a lithium clearance technique and measuring urinary enzyme levels Nine patients with metastatic colorectal cancer were treated with rIL-2, 18×10^6 units per m^2 body surface area per 24 h, by continuous intravenous infusion for 120 h Lithium clearance was measured before starting rIL-2 infusion (day 0), after 48 h of treatment (day 3), 36 h following cessation of rIL-2 treatment (day 7) and finally 3 weeks later Urinary activities of alanine aminopeptidase (AAP), gamma glutamyl transferase (GGT) and *N*-acetyl-β-D-glucosaminidase (NAG) were also measured daily

	Day 0	Day 3	Day 7
Serum creatinine (μmol l^{-1})	77(4)	89(8)	84(6)
Creatinine clearance (ml min^{-1})	90(11)	49(6)*	72(13)*
Lithium clearance (ml min^{-1})	27(4)	10(2)*	11(3)*
Sodium clearance (ml min^{-1})	0·9(0·2)	0 1(0 1)*	0·22(0 07)
Fractional sodium excretion (%)	1 2(0·3)	0 3(0 1)*	0 5(0 2)*
Fractional lithium excretion (%)	29 6(3·1)	18 2(4 7)*	15 3(3·1)*
Urinary enzyme levels (units per mmol urinary creatinine)			
AAP	3(3)	18(9)*	15(8)*
GGT	6(4)	21(11)*	22(6)*
NAG	44(5)	105(5)*	52(10)

Values are mean(s.e.m.) $*P<0 005$ *versus* day 0

By 3 weeks after treatment the abnormalities in glomerulotubular function showed a return towards pretreatment values, although certain measures of handling of sodium and water by the nephron remained abnormal These measurements demonstrate alterations in proximal and distal nephron function during rIL-2 therapy and may allow further understanding of the pathogenesis of rIL-2-induced renal dysfunction

Verapamil is beneficial in a model of acute pancreatitis after endoscopic retrograde cholangiopancreatography

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Acute pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) is an ischaemic injury. The calcium-blocking drug verapamil ameliorates ischaemic small intestinal damage This study assessed the effect of verapamil in an experimental model of acute pancreatitis after ERCP. A group of 38 male Sprague-Dawley rats (300 g) were anaesthetized and acute haemorrhagic pancreatitis induced by retrograde injection of 0 2 ml 4 per cent sodium taurocholate over 60 s into the pancreatobiliary duct Serum amylase was estimated before the onset of pancreatitis and at 24 h. Animals were randomized into four groups and 1 ml saline or verapamil (1 g kg^{-1}) administered intramuscularly Group 1 received saline and group 2 verapamil, before induction of pancreatitis; group 3 received saline and group 4 verapamil, administered 2 h after induction of pancreatitis Survival was observed to day 7 All pancreatic specimens were examined histologically after post-mortem examination Differences were analysed by Student's *t* test for serum amylase and Fisher's exact test for survival

		Amylase (units)*		
Group	*n*	0 h	24 h	Survival†
1	12	4100(872)	12 700(3555)	4 (33)
2	10	3905(900)	7 305(1236)	9 (90)‡
3	8	4231(649)	12 143(1662)	3 (38)
4	8	3581(679)	12 400(1881)	4 (50)

*Values are mean(s e m); †values in parentheses are percentages ‡$P<0 05$ *versus* group 1

All rats had hyperamylasaemia following taurocholate injection and this was unaffected by verapamil administration Pancreatitis was confirmed histologically in all animals Calcium blockade with verapamil successfully ameliorated acute pancreatitis but delayed treatment was not effective Verapamil may have a role in the prophylaxis of pancreatitis following ERCP.

Bacterial translocation in obstructive jaundice

J.V. Reynolds, P. Murchan, N. Leonard, D.B. Gough, P. Marks, F B.V. Keane and W.A Tanner, *Department of Surgery, Meath Hospital and Trinity College, Dublin, Ireland*

Bacterial translocation is the passage of viable resident bacteria, usually Gram-negative aerobes, from the gastrointestinal tract to normally sterile tissues such as the mesenteric lymph nodes (MLNs) Current concepts of the endogenous origin of sepsis in critically ill patients suggest that translocation of bacteria is the first step triggering the cytokine-mediated septic state. Mechanisms underlying sepsis in jaundiced patients are not clear and this study addressed the relevance of bacterial translocation.

Sprague-Dawley rats ($n=77$) underwent laparotomy and division of the bile duct ($n=41$) or sham ligation ($n=36$). At 24 h, 1 week and 3 weeks, animals from each group were killed, the MLN complex and caecum excised, and cells cultured using standard bacteriological techniques

Five bile duct-ligated rats (12 per cent) died between 2 and 3 weeks Translocation to the MLNs at each time point and caecal *Escherichia coli* levels at 3 weeks were as shown

	Translocation to MLNs			
Group	24 h	1 week	3 weeks	Mean(s e.m) *E. coli*
Sham	0 of 8	0 of 10	0 of 18	$1(1) \times 10^6$
Ligated	0 of 8	8 of 12*	6 of 16*	$10(2) \times 10^6$*

$*P<0 001$ *versus* sham (Student's *t* test)

Biliary obstruction significantly promotes bacterial translocation The effect is maximal at 1 week and the mechanism may correlate with intestinal overgrowth of *E coli* The theory of gut-origin sepsis is relevant to obstructive jaundice and therapies targeted toward decreasing bacterial translocation merit experimental evaluation in the prophylaxis of biliary sepsis

Preoperative rise and postoperative consumption of antiendotoxin antibodies in jaundiced patients

D.C. McCrory, M.I. Halliday, M. McCaigue, G R. Barclay* and B J Rowlands, *Department of Surgery, The Queen's University of Belfast and *Blood Donor Centre, Edinburgh, UK*

Despite the postulated importance of endotoxin in the development of complications in jaundiced patients, it has been found only sporadically in clinical studies Antibodies produced in response to endotoxin will persist long after endotoxin exposure owing to their longer half-life

Plasma samples were obtained from 19 jaundiced and 11 control patients at four time points before surgery and 1 day, 1 week and 4 weeks after surgery Immunoglobulin (Ig) G and IgM anticore glycolipid (anti-CGL) antibodies were measured by enzyme-linked immunosorbent assay.

	IgG				IgM			
Group	Preop	Day 1	Week 1	Week 4	Preop	Day 1	Week 1	Week 4
Jaundice	274(56)†	202(40)*	273(59)	310(71)*†	88(14)	76(15)*	96(23)	84(14)
Control	114(15)	120(20)	122(17)	127(18)	74(13)	69(11)	68(11)	54(8)

Values are mean(s e m) anti-CGL levels $\dagger P<0 05$ *versus* control group (Mann-Whitney *U* test), $*P<0 05$ *versus* preoperative value (ANOVA)

It is concluded that the increase in IgG anti-CGL before surgery indicates chronic endotoxin exposure The fall in both IgG and IgM anti-CGL on day 1 after surgery is due to consumption of antibodies by an endotoxin pulse released at operation. The IgG anti-CGL level rises at 4 weeks in response to this These results emphasize the need for specific antiendotoxin therapies in jaundiced patients They demonstrate that anti-CGL is an excellent indicator of both chronic and acute endotoxin exposure

Alterations in renal haemodynamics may predict the presence of hepatic micrometastases

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Previous work has shown that the rise in the hepatic perfusion index (HPI) in the presence of overt tumour in the rat is accompanied by a significant decrease in renal blood flow (RBF). As there is little information on the temporal relationship between alterations in RBF and the growth and development of hepatic tumour, such a study has been undertaken in the rat Male Fisher rats received an intraportal injection of $1 \cdot 6 \times 10^7$ Walker cells and controls the same number of dead cells. RBF and hepatic blood flow were measured by the microsphere method and by dynamic scintigraphy 2, 4, 6 and 21 days after intraportal administration of viable or dead cells Micrometastases were present histologically at 4 days and the mean(s e m) HPI (51·8(1 68)) was significantly greater ($P<0\,0001$, Mann–Whitney U test) than in controls (33 78(1·77)). The increase in the HPI at 4 days was accompanied by a significant increase in the mean(s.e m) renal transit time (3 95(1 18) s) compared with controls (2·28(0 48) s) Conversely, the RBF was significantly reduced in animals with micrometastases (7·32(2 81) ml min^{-1}) compared with controls (14 02(3 42) ml min^{-1}). These changes in HPI, renal transit time and RBF were maintained at 6 and 21 days These results suggest that RBF is reduced during the early stages of growth and development of hepatic tumour. Furthermore, as renograms with a flow phase are technically easier to perform in humans than estimations of the HPI, determination of RBF may be of value in the detection of occult liver metastases

Photodynamic ablation of the gallbladder mucosa

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Minimally invasive methods of gallbladder stone removal do not prevent recurrence of these stones unless the gallbladder mucosa is destroyed Chemical destruction of the gallbladder mucosa requires reliable cystic duct occlusion The feasibility of photodynamic gallbladder mucosal ablation was investigated in 18 New Zealand White rabbits. Animals were given 15 mg kg^{-1} polyhaematoporphyrin (PHP) 4 h before light exposure Controls had saline injection. Under intravenous general anaesthesia, the rabbit gallbladders were surgically dissected and exposed to light from an argon laser at 50 mW cm^{-2} for 15 min (total energy delivered 50 J) Controls received no light After 2 weeks, the rabbits were killed and gallbladders removed for histological assessment by an independent pathologist Gallbladders from animals receiving PHP followed by laser light showed complete mucosal destruction in all cases Rabbits that underwent surgery alone or those that received PHP alone had intact gallbladder mucosa. It is concluded that gallbladder mucosal ablation with photodynamic therapy appears to be feasible and may have a role in the management of gallstones, especially as topical photosensitizers and portable laser equipment become available.

Herbimycin A inhibits the growth of human pancreatic cancer cells *in vitro*

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Epidermal growth factor (EGF) stimulates proliferation through interaction with its membrane receptor, which has intrinsic tyrosine kinase activity. This leads to phosphorylation of the receptor itself and cellular substrate proteins. EGF receptor overexpression occurs in human pancreatic carcinoma cells and this, together with the autocrine production of transforming growth factor alpha, may provide a mechanism for unregulated proliferation. Herbimycin A (HMA) is a potent inhibitor of protein tyrosine kinases, the effects of HMA on the proliferation of two pancreatic cancer cell lines (MiaPaCa-2 and Panc-1) were therefore examined.

Cells were serum-deprived for 24 h, then cultured with serum-free medium containing 10^{-8} mol l^{-1} EGF or medium containing 10 per cent serum Cell proliferation was determined by uptake of [^{3}H] thymidine at 48 h of culture.

Mean(s.e.m) control values (c.p.m) were: MiaPaCa-2 – 3937(81) (EGF), 74341(1379) (serum); Panc-1 – 875(34) (EGF), 16178(605) (serum).

Cancer cell line	HMA (mol l^{-1})				
	10^{-8}	5×10^{-8}	10^{-7}	5×10^{-7}	10^{-6}
MiaPaCa-2					
EGF	4·3(4·7)	40·8(4·4)*	86·7(0·9)*	98·5(0·5)*	98·2(0·4)*
Serum	3·8(2·9)	25·7(1·5)*	79·2(1·0)*	99·9(0·0)*	99·9(0·0)*
Panc-1					
EGF	1·2(1·8)	18·0(2·1)*	38·7(2·2)*	85·3(2·5)*	94·0(0·7)*
Serum	6·3(3·4)	5·4(2·2)	8·1(2·2)	58·9(1·9)*	91·2(0·6)*

Values are expressed as mean(s e m) percentage decrease from controls $^*P<0\cdot01$ *versus* control (Student's *t* test)

HMA caused a dose-dependent inhibition of pancreatic cancer cell growth *in vitro* HMA toxicity (percentage non-viable cells assessed by trypan blue) was <1 per cent for serum-stimulated cells except for MiaPaCa-2 at 5×10^{-7} mol l^{-1} (18 per cent) and 10^{-6} mol l^{-1} (20 per cent) It is concluded that HMA, because of its inhibitory effects on tyrosine kinases and low toxicity, may have a role as an antiproliferative agent in pancreatic cancer.

Symptomatic outcome 1 year after laparoscopic cholecystectomy

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It has been speculated that the symptomatic outcome after laparoscopic cholecystectomy (LC) may be better than after open cholecystectomy (OC) To assess this a standard questionnaire was sent to 100 patients who had LC 12 months or more previously. The same questionnaire was sent to patients who had OC ($n=167$) and inguinal hernia repair (IH) ($n=163$) in the same unit at least 12 months before Patients were asked to classify frequency of selected symptoms experienced in the preceding 6 months as 'every day', 'most days', 'occasionally' or 'never', a technique previously used by the authors to assess outcome after duodenal ulcer surgery The percentages having symptoms every day or most days and patients' assessments are shown.

Symptom	LC ($n=100$)	OC ($n=167$)	IH ($n=163$)
Stomach pain	6	6·6	6·1
Nausea or vomiting	10	3·6	5·0
Heartburn	14	9·6	10·4
Bloating	12	14·3	5·0
Flatulence	17	20·3	14·1
Antacid consumption	23*	12·0	15·3
Operation a success	94	95·2	94·4
Symptoms cured or improved	94	94·0	94·4

Values are percentages $^*P<0\cdot05$ *versus* OC

There was no significant difference in the number of patients who considered their operation a success and their symptoms cured or improved The patients who had LC consumed significantly more antacids and had a higher incidence of nausea or vomiting than those who had OC. It is concluded that no long-term symptomatic advantage is gained by patients undergoing LC compared with conventional OC.

Polyunsaturated fatty acids inhibit the growth of human pancreatic cells *in vitro*

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Polyunsaturated fatty acids have recently been shown to inhibit the growth of a variety of malignant cell lines and have been suggested as novel agents in cancer chemotherapy. Currently there is no effective treatment for patients with irresectable pancreatic cancer The effect of a variety of fatty acids on the growth of human pancreatic cancer cell lines MiaPaCa-2, Panc-1 and Cf-Pac has been investigated. Cells were grown in media supplemented with increasing physiological concentrations (0–40 μmol l^{-1}) of fatty acids bound to albumin, to find the mean inhibitory dose (ID) of each fatty acid The mean ID_{10}, ID_{50} and ID_{90} for the three cell lines tested are shown. Also shown is the modifying effect of an antioxidant (vitamin E) on the growth inhibition achieved.

Fatty acid	ID_{90}	ID_{50}	ID_{10}	ID_{50} plus vitamin E*
Eicosapentanoic acid	20	2·5	<1·25	>30
Docosahexanoic acid	—	20	7	
Gamma linolenic acid	—	30	11	
Oleic acid	—	—	—	

Values are expressed as μmol l^{-1}. —, ID not achieved within concentration range tested (0–40 μmol l^{-1}); *vitamin E concentration 8 μmol l^{-1}

Eicosapentanoic acid is the most potent inhibitor of the pancreatic cancer cell lines tested. Moreover, this effect appears to be mediated by lipid peroxidation (cf. vitamin E effect). It is concluded that eicosapentanoic acid may offer a novel means of anticancer therapy in pancreatic cancer but that antioxidants in the patient's diet may strongly modify any potential benefit

Effect of cryosurgery on blood flow in normal liver and liver tumour in the anaesthetized rat

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The mechanism of tissue necrosis following cryosurgery is uncertain. Circulatory shutdown resulting in hypoxia may occur. The effect of cryosurgery on liver blood flow was investigated using laser Doppler velocimetry. Home Office approval was obtained for all experiments.

A total of 24 male Wistar rats, mean(s.e.m.) weight 200(10) g, underwent laparotomy: 12 animals were injected with 10^5 cells of a rat fibrosarcoma into the left lateral lobe of the liver; the remaining 12 were controls. After a second laparotomy 14 days later, cryosurgery was performed using a Frigitronics cryounit in tumour-bearing ($n=6$) and control ($n=6$) animals. The remaining animals ($n=12$) underwent sham cryosurgery. Red cell flux (RCF) was recorded at the site of tumour or equivalent in controls using a Perimed laser Doppler velocimeter before and immediately after cryosurgery or sham procedure. A further laparotomy was performed 2 weeks later and RCF measured in the same location before the animals were killed

	Before cryosurgery	After cryosurgery
Tumour plus cryosurgery	70(8)	9(9)*
Control plus cryosurgery	66(8)	0*
Tumour plus sham	91(6)	93(7)
Control plus sham	74(10)	77(12)

Values are mean(s.e.m.) *$P<0·05$ (Mann–Whitney U test)

Cryosurgery caused vascular shutdown in the liver irrespective of pathology, whereas control procedures had no effect. By 2 weeks the flow had returned to normal. Further studies have shown that the reduction in flow lasted for at least 8 h but had recovered by 24 h. This initial reduction in blood flow may contribute to the efficacy of cryosurgery

SURGERY ABSTRACTS

Br. J. Surg. 1992, Vol. 79, November, 1244–1245

For the past 4 years or so The British Journal of Surgery *has pursued a closer relationship with the American journal* Surgery. *In 1989 we began publishing each other's list of contents, and later that year embarked on the experiment of reproducing one article from each other's issue. Neither measure was entirely satisfactory, but our wish for friendly links remains strong. This month we present a selection of abstracts from papers that have recently appeared in* Surgery, *and that journal will reciprocate. The Editors welcome the views of readers on this scheme, which has been introduced for a trial period.*

Photoplethysmography reexamined: Lack of correlation with duplex scanning

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In a prospective study a comparison was made between the results of photoplethysmography and ultrasonic duplex scanning in 151 consecutive legs with swelling, aching, and suspected venous insufficiency. Thirty-four percent of the legs had a history of previous deep venous thrombosis, 26% had undergone previous superficial vein surgery, and 11% had active or healed ulceration. Photoplethysmographic findings were normal in 86 (57%) of these legs and indicated deep venous disease in 33 (22%). With duplex scanning, incompetent vein segments were found in 140 legs (93%). The κ coefficient of agreement between the result, classified as either normal, superficial disease only, or deep incompetence, was 0.12 ± 0.06. In legs with superficial disease, the number of incompetent levels was no greater in legs with abnormal results of photoplethysmography than in legs with normal results of photoplethysmography. In general, an abnormal photoplethysmographic result is related to multilevel reflux and the presence of visible skin changes. Photoplethysmography had the same value, in these patients, to predict the presence of multilevel reflux as had inspection of the skin of the gaiter area. These results do not warrant the continued use of photoplethysmography for surgical decision making in patients with suspected venous insufficiency. (Surgery *1992;112:544-8.)*

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Long-term follow-up of patients with node-negative breast cancer treated only by regional therapy

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Background. *This study examines the potential impact of intercurrent diseases on survival after adjuvant chemotherapy for node-negative (N_0) breast cancer in light of 30-year follow-up results in 136 patients with N_0 disease receiving only regional therapy at the University of Texas M.D. Anderson Cancer Center between 1958 and 1960.*

Methods. *We made a retrospective review of treatment records.*

Results. *Thirty-nine women (28.6%) died of the initial breast cancer, including 12 (22%) of 54 premenopausal women, 15 (43%) of 35 perimenopausal women, and 12 (25%) of 47 postmenopausal women ($p \leq 0.09$). Six (12%) of 49 patients with T_1 disease died of the initial breast cancer versus 27 (38%) of 70 patients with T_2 disease and 6 (35%) of 17 patients with T_3 disease ($p \leq 0.006$). Five of 10 women died of metachronous contralateral breast primary lesions. Deaths from other cancers occurred in 11%, 2.8%, and 6.4% of premenopausal, perimenopausal, and postmenopausal women, respectively. Deaths from nonmalignant conditions occurred in 22%, 20%, and 59% of premenopausal, perimenopausal, and postmenopausal women, respectively. Overall survival at 30 years was 35 (26%) of 136 patients.*

Conclusions. *Given these statistics, if one postulates that adjuvant chemotherapy reduces the death rate from an initial breast cancer by 30% to 77% (estimates based on data from adjuvant chemotherapy trials in patients with N_+ or N_0 disease), a 5% to 12.9% increase in the 30-year survival would have resulted.* (Surgery *1992;112:689-93.)*

From the Departments of General Surgery and Biomathematics, University of Texas M.D. Anderson Cancer Center, Houston, Texas, and the University of Illinois Specialized Cancer Center, Chicago, Ill.

Functional analysis of monocyte activity through synthesis patterns of proinflammatory cytokines and neopterin in patients in surgical intensive care

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This study was designed to further differentiate monocyte behavior in critically ill patients with operative or accidental trauma. The patient population studied consisted of 39 patients (17 patients undergoing elective surgery [ES], seven patients with major multiple injuries [MI], and 15 patients in *an acute septic state [S]). Immunologic parameters assessed included monocyte phenotyping with the monoclonal antibody LeuM3, measurement of the cytokines interleukin (IL)-1, IL-6, and IL-8 in lipopolysaccharide-stimulated in vitro cultures of mononuclear leukocytes (PBMCs), and determination of neopterin in γ-interferon–stimulated in vitro cultures and corresponding serum samples. Serum neopterin levels were very high in S patients (89.0 nmol/L; $p > 0.05$) compared with control values (4.6 nmol/L), with a rise to 16.4 nmol/L in ES patients on day 7 and 13.4 nmol/L in MI patients on day 7. The concentrations of γ-interferon–induced neopterin in the supernatants of the PBMC cultures were elevated in all patient groups. Severe impairment of IL-1 synthesis was seen in MI and S patients. IL-8 synthesis (818 ± 150 units/ml, control value) was also suppressed ($p < 0.05$) in MI patients; the values were 135 ± 65 units/ml on day 1, 231 ± 110 units/ml on day 3, 347 ± 131 units/ml on day 7, and 355 ± 107 units/ml in S patients. The kinetic patterns of synthesis were comparable for IL-1 and IL-8 in all patient groups. Lipopolysaccharide-induced IL-6 synthesis ($9.4 \pm 1.5 \times 10^3$ units/ml, control value) was significantly elevated in the PBMC cultures of all patient groups, with the exception of the early phase after accidental trauma. Maximum amounts of IL-6 synthesis after surgery were $19.6 \pm 7 \times 10^3$ units/ml in S patients and $19.0 \pm 2.2 \times 10^3$ units/ml in ES patients. These results demonstrate (1) the impairment of the functional capacity of circulating monocytes and (2) that the degree of functional impairment is proportional to the severity of the injury. (SURGERY 1992;112:562-72.)*

From the Department of Surgery, Ludwig-Maximilians-University, Klinikum Großhadern Munich, and Gesellschaft für Strahlen- und Umweltforschung, Institut fur Experimentelle Haematologie Munich, Munich, Germany, Ludwig-Boltzmann Institut für Experimentelle und Klinische Traumatologie, Vienna, Austria, and Theodor Kocher Institute, Bern, Switzerland

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Radioimmunoguided surgery challenges traditional decision making in patients with primary colorectal cancer

Mark W. Arnold, MD, Schlomo Schneebaum, MD, Angie Berens, BSN, RN, Cathy Mojzisik, MS, RN, George Hinkle, MS, RPh, *and* **Edward W. Martin, Jr., MD,** *Columbus, Ohio*

Background. *Initial experience with the radioimmunoguided surgery system (RIGS) has been found to impact on decision making in patients with recurrent colorectal cancers. Reported here is experience with RIGS-influenced therapeutic decisions in patients with primary colorectal cancer.*

Methods. *Thirty-six evaluable patients with primary cancers were injected with the second-generation anti-tumor-associated glycoprotein antibody CC49 labeled with 1 to 2 mCi iodine 125. Pharmacokinetic determination and precordial counts were obtained after injection and weekly until levels were less than 20 counts/2 sec. At surgery abdominal and pelvic explorations were performed, first traditionally by inspection and palpation and then with the hand-held, γ-detecting probe. RIGS-positive tissue was considered cancerous and removed if possible*

Results. *Thirty patients (83%) had positive antibody localization at surgery. Of those patients with localization, in 24 (80%) additional information was obtained at the time of surgery. In 11 patients (34%) staging changes were made as a result of RIGS exploration. New findings resulted in operative changes in nine patients (25%). Eleven (30%) of the original 36 patients became eligible for adjuvant chemotherapy based on current recommendations because of RIGS findings.*

Conclusions. *In conclusion, the RIGS system provides immediate staging information that impacts on therapeutic interventions, challenging the adequacy of traditional procedures alone for primary colorectal cancer exploration. (SURGERY 1992;112:624-30.)*

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Familial nonmultiple endocrine neoplasia medullary thyroid carcinoma: An evolving clinical entity

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Background. *A rare kindred of familial nonmultiple endocrine neoplasia medullary thyroid carcinoma arising from a 73-year-old proband case is reported to further define this distinct entity.*

Methods. *Twenty-four family members across four generations, four with medullary thyroid carcinoma (MTC) and two with C-cell hyperplasia (CCH), were studied.*

Results. *Basal calcitonin levels were elevated in three patients with MTC and were normal in one patient with microscopic MTC and two patients with CCH who had persistent subtle elevation in calcium and/or pentagastrin-stimulated calcitonin levels. One patient had unilateral MTC without CCH. Associated abnormalities included papillary carcinoma (2), thyroiditis (4), adenoma (2), and colloid nodule (1). Minimum treatment was total thyroidectomy. Two patients with MTC and marked hypercalcitonemia have recurrent disease at 2 5-year and 11-year follow-up. Two patients with MTC and normal or minor elevations in basal calcitonin and two with CCH had normal provocative calcitonin testing at 6 to 18 months follow-up.*

Conclusions. *Unilateral MTC without CCH and MTC in the elderly do not preclude a familial cause. Microscopic MTC or CCH may be seen with subtle elevations in stimulated calcitonin levels, and recognition allows for curative thyroidectomy. Other apparent dominant thyroid pathologic conditions may occur concomitantly with familial medullary thyroid carcinoma and thus routine calcitonin, and immunohistochemical testing should be performed in patients with an appropriate family history. (SURGERY 1992;112:728-33.)*

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Correspondence

Evaluation of tissue oximetry in perioperative monitoring of colorectal surgery

Sir

We read with interest the recent article by Van Esbroeck and colleagues on tissue oximetry in colorectal surgery (*Br J Surg* 1992; **79**: 584–7) We wish to raise a number of points about this paper. The introduction states that 'subcutaneous tissue partial pressure of oxygen (P_{scO_2}) .. correlate(s) more accurately with haemodynamic status than traditional perfusion parameters', but no reference is given to support this claim. In *Patients and methods* it is stated that gastric intramural pH (pH_i) was measured according to the method of Fiddian-Green and Baker The reference is not written exactly according to the guidelines laid down in the Journal's Instructions to Authors, and the paper referenced does not describe the method of measuring pH_i[1] In the next paragraph in the article, arterial hypoxaemia is defined as an arterial partial pressure of oxygen (P_{aO_2}) of 80 mmHg or an oxygen saturation <90 per cent. These values are not comparable: an oxygen saturation of 90 per cent[2] would generally indicate a P_{aO_2} of 60 mmHg. The controls are not age matched with the patients, making comparison of tissue perfusion difficult. Was there an attempt to adjust statistically for age?

In the *Discussion* it is stated that there was a significant difference between preoperative and postoperative P_{scO_2} values, but the subcutaneous oximeters were inserted at the time of surgery, not before operation. Was there a significant difference between the complicated and uncomplicated patients in relation to postoperative P_{scO_2}, as this was not mentioned in the *Results*?

We feel that this study (while conceptually important) should be of larger numbers, with appropriate matched controls, and have stratification of the complication endpoints before any valuable conclusion can be reached.

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1 Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. *Crit Care Med* 1987; **15**: 153–6.
2 Ganong WF. Gas transport between lung and tissue In: Ganong WF, ed. *Review of Medical Physiology* Los Altos: Lange Medical, 1981: 520–6.

Authors' reply

Sir

We thank Mr Sugrue and co-workers for their interest in our paper. They suggest that we stated that there was a significant difference between preoperative and postoperative subcutaneous partial pressure of oxygen values Careful reading shows that this is not the case Measurements were made only in the peroperative and postoperative periods; this was clearly stated. Moreover, one of the most puzzling results of our study is that there is a significant difference between peroperative subcutaneous oxygen tensions of the uncomplicated and complicated patient groups. There was no such difference after operation. One might almost suggest that the patients had their postoperative complications in the operating theatre.

If peripheral tissue oximetry is made simpler and quicker to perform, larger numbers of patients will indeed be studied with appropriate matched controls.

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Technique for laparoscopic appendicectomy

Sir

We read with interest the recent Surgical Workshop by Byrne and colleagues describing their technique for laparoscopic appendicectomy (*Br J Surg* 1992, **79**: 574–5). We use a similar technique and support their assertion that laparoscopically guided dissection and delivery of the appendix on to the abdominal surface is safe and can be learned quickly.

Our technique is different in two important ways. First, we deliver the appendix through a standard non-disposable 10-mm trocar and cannula Second, we ligate the appendix stump and vessels, and never use staplers. We believe that employing disposable trocars and cannulas and the use of stapling devices defeats the major financial advantage of this technique for appendicectomy over intra-abdominal procedures, which involve the use of endo-clips and endo-staplers. The technique described by Byrne and colleagues uses at least one disposable trocar and cannula (perhaps two – their article does not make it clear) and one TA30 stapler (Auto Suture, Ascot, UK). The extra cost of disposables when compared with conventional open appendicectomy is well over £100 and is an important objection to their method.

We have noted that once the appendix is withdrawn through the cannula, it can be difficult to identify the junction between appendix and caecum. With traction on the appendix, the caecum can be 'tented' and we have on one occasion inadvertently tied the caecum. We now mark the proposed site of appendix ligation by briefly touching the appendix with diathermy. Once the appendix is delivered, it is easy to identify the serosal diathermy mark We inspect the caecum and appendix stump within the abdominal cavity, after appendicectomy, confirming that all the ligatures are secure.

We recommend our modifications: costly disposables are not used, ligatures are easily tied on the abdominal surface and the site of appendix ligation can be confidently identified

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Cholecystectomy and gallbladder conservation

Sir

We agree entirely with the suggestion of Messrs Walsh and Russell (*Br J Surg* 1992; **79**: 4–5) that gallbladder conservation is a desirable option in the management of gallbladder stone disease and have read with interest Mr Salam's comments (*Br J Surg* 1992; 79: 713) regarding laparoscopic cholecystotomy and stone removal Surgical laparoscopy requires general anaesthesia and a formal pneumoperitoneum, and whether this is 'minimally invasive' is open to debate. We have described a simple and safe technique for gallstone removal under local or regional anaesthesia[1]. The whole procedure is conducted under direct vision and the complications of a 'blind' entry into the peritoneum are also avoided.

We agree with Mr Salam's suggestion that gallbladder conservation in contracting gallbladders be compared with cholecystectomy, as the incidence of stone recurrence may not be nearly as high as is often assumed[2].

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1. Majeed AW, Reed MWR, Watkin DFL, Smart JG, Johnson AG. Sheffield Cholecystoscope: new instrument for minimally invasive gallbladder surgery. *Br J Surg* 1991; **78**. 557–8.
2. Cheslyn-Curtis S, Donald J, Ainley C, Lees WR, Russell RCG. Gallstone recurrence following cholecystolithotomy. *Br J Surg* 1990, **77**: 1423 (Abstract).

Easy delivery of the gallbladder in laparoscopic cholecystectomy: a grooved director

Sir

Further to the recent Surgical Workshop (*Br J Surg* 1992; **79**: 344) about the best method of retrieving the detached gallbladder from the peritoneal cavity at the end of laparoscopic cholecystectomy, we have found the most effective technique is to employ an otology speculum. This instrument is inserted into the subumbilical wound after withdrawal of the laparoscopic cannula, and a grasping forceps is passed through it to secure the gallbladder. The speculum can be opened to the required size to permit withdrawal of the gallbladder.

This technique has proved to be straightforward in practice and does not require the manufacture of a specialized instrument, as the speculum is readily available in any hospital that has an ear, nose and throat department

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M. J. Kelly

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UK

Necrotizing fasciitis: 10 years' experience in a district general hospital

Sir

The 10-year audit by Ward and Walsh of necrotizing fasciitis presenting to a district hospital in the UK (*Br J Surg* 1991; **78**: 488–9) produced 14 patients for analysis. The authors commented that this is an uncommon condition.

At the University Teaching Hospital, Lusaka, Zambia, on just one of five general surgical and trauma units in the first 4 months of 1991 we cared for six patients with necrotizing fasciitis. Two followed ischiorectal abscesses, one was of apparently spontaneous onset in the lower limb of a human immunodeficiency virus (HIV)-seropositive patient, one followed a colonic gunshot wound, one spontaneous extravasation of urine proximal to a urethral stricture, and the sixth followed a vaccination abscess in a 10-month-old infant No patient was diabetic, two were HIV antibody seropositive.

The authors of the article excluded Fournier's gangrene. In Zambia, where scrotal necrotizing fasciitis usually presents late with fasciitis extending widely on to the abdominal wall and sometimes on to the thighs, it is clear that the distinction is arbitrary, and that Fournier's gangrene is just one of the eponyms by which necrotizing fasciitis has become known[1].

In the authors' recommended management they omit one important modality, namely correction of anaemia. Patients are frequently anaemic on admission and lose blood heavily during the major debridements that are necessary.

As the authors observe, necrotizing fasciitis can be easily recognized clinically by the grey necrotic fascia but, as similar fascia can be seen in pressure sores and gangrenous pyoderma, the important clinical feature is that in necrotizing fasciitis the grey necrotic unhealthy fascia extends beneath apparently healthy skin well beyond the margin of the wound. Diagnosis and determination of how far debridement will have to extend can be helped by stab incisions away from the wound margin.

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1. Roberts JO, Fenton OM, Peters JL. Necrotising fasciitis. *Hospital Update* 1985; **11**: 289.

Retroperitoneal necrotizing fasciitis

Letter 1

Sir

Woodburn *et al.* (*Br J Surg* 1992, **79**: 342–4) linked the high mortality rate associated with retroperitoneal necrotizing fasciitis to delayed diagnosis caused by the late manifestation of the latter in the overlying cutaneous tissues as well as a lack of means for earlier diagnosis

I have dealt with several cases of Fournier's gangrene with retroperitoneal involvement and have found that an infarcted gangrenous testis is a good and early sign of retroperitoneal necrotizing fasciitis. The testicular blood supply is thrombosed early in the course of retroperitoneal involvement and a gangrenous testis is an indication for laparotomy with a view to retroperitoneal debridement

F. Seow-Choen

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Letter 2

Sir

We read with much interest the article by Woodburn *et al.* on retroperitoneal necrotizing fasciitis (*Br J Surg* 1992, **79**: 342–4) and feel that they have presented the problem well. In view of the terrible mortality rate they report for retroperitoneal fasciitis, we would like to describe a case that demonstrates that survival is possible in younger patients who are treated aggressively

A 28-year-old nurse presented with a 6-day history of increasing abdominal pain with signs of peritonitis. After resuscitation and under appropriate antibiotic cover a perforated appendix was removed and the peritoneal cavity was thoroughly lavaged with saline. Culture of the intra-abdominal pus yielded *Streptococcus milleri* and *Bacteroides* sp. She was making a slow recovery when, 1 week later, the wound began to discharge copious amounts of pus. This grew *Pseudomonas aeruginosa*, and intravenous ciprofloxacin and benzylpenicillin were added to the regimen.

Pus continued to drain and 4 days later the abdominal wound was explored under general anaesthesia. This revealed extensive necrotizing fasciitis of the subcutaneous tissues of the abdominal wall from the right to left flank. Over 2 litres of pus were drained and the dead abdominal wall skin and muscle were debrided. The abscess continued deep into the extraperitoneal tissues in the right iliac fossa. Cultures of the pus once again yielded *S milleri* and *Bacteroides* sp., in addition to *Escherichia coli* Following this extensive debridement the patient showed an initial improvement However, 10 days later large quantities of small bowel contents were discharged from the original wound site Abdominal computed tomography (CT) revealed multiple intra-abdominal abscesses. Her condition declined despite intensive antibiotic therapy and repeat CT showed obvious necrotizing fasciitis of the retroperitoneal tissues with extension of the intra-abdominal collections.

At laparotomy the fistula was found to come from a necrotic area of caecum. An ileocaecal resection was performed and a defunctioning ileostomy was raised. The intra-abdominal abscesses were drained and the abdomen again thoroughly lavaged with saline. The patient's condition improved gradually and repeat CT 10 days later showed no residual necrosis or collections. She was discharged 9 weeks after initial admission A subsequent admission for reversal of the stoma was uneventful and she has now returned to full health.

This case illustrates the value of CT in determining the presence and extent of retroperitoneal fasciitis and the timing of subsequent surgical procedures It also demonstrates that survival in this deadly condition is dependent on the successful eradication of the source of sepsis

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J. R. Novell
A. A. M. Lewis

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Mechanism of action of external compression on venous function

Sir

The article on compression and venous function by Sarin *et al.* (*Br J Surg* 1992; **79**: 499–502) failed to address issues raised by myself[1,2] and Wood[3], which showed the importance of maintaining external support at precisely the same level as the intravascular pressure in all postures. Such hydrostatic stockings or 'G' suits theoretically compensate for postural changes. The mechanism of external support therefore does not apply solely to veins, but also to arteries and capillaries.

A. D. B. Chant

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1. Chant ADB. Compression and limb blood flow. *BMJ* 1970; **ii**. 235–6.
2. Chant ADB The effects of posture, exercise and bandage pressure on the clearance of ^{24}Na from the subcutaneous tissues of the foot *Br J Surg* 1972; **59** 552–5.
3. Wood JE The venous system *Sci Am* 1968; **218**(1)· 86–96

Authors' reply

Sir

In our paper we were trying to determine the role of compression on the large veins of the lower limb Compression may or may not have an effect on arteries and capillaries but our work was not designed to examine that question. Theorizing on the value of 'G' suits was considered inappropriate and therefore not addressed

We have recently been investigating the effects of compression on the cutaneous microcirculation and have found a pronounced effect for similar levels of compression as achieved by commercial hosiery We would agree with Mr Chant that the influence of compression on all components of the circulation should be investigated

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P. D. Coleridge Smith

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Function of the distal rectum after low anterior resection for carcinoma

Sir

I am very uneasy with the conclusion reached by Karanjia, Schache and Heald (*Br J Surg* 1992; **79**: 114–16). The authors selected two groups of patients with stapled anastomosis at median distances of 3 and 6 cm from the anal verge and found that postoperative anal function was superior in those with the higher anastomosis They then concluded that this improvement in functional outcome justifies conservation of the distal rectum, and that as much of the distal rectum as possible should be preserved during very low anterior resection, while stressing total mesorectal clearance in the same breath.

I agree that it is oncologically possible to reduce the distal margin of clearance to 1 cm during anterior resection and not see an increase in local recurrence rate However, the preservation of as much rectum as possible after complete mobilization of the rectum with total mesorectal clearance and division of the lateral ligaments is not in accord with sound surgical principles These manoeuvres tend to devascularize the rectal stump, the preservation of as much rectum as possible may therefore leave an ischaemic rectal stump with a higher risk of anastomotic breakdown Indeed this is borne out in the authors' paper. There was one leak in 27 patients (4 per cent) where the anastomosis was 3 cm from the anal verge, but were significantly more leaks (five in 56 patients; 9 per cent) where the anastomosis was at 6 cm.

Improved postoperative anal function is better achieved with the use of the colonic pouch rather than leaving possible ischaemic rectal stumps in very low anastomosis[1,2] In a prospective randomized trial currently being conducted in this department with 19 patients to date, median frequencies of bowel movement per 24 h of 2 (range 0–5) and 5 (range 2–15) were obtained for pouch–anal and straight anastomoses respectively 1 month after ileostomy closure. The median distance from the anal verge to the anastomosis was 3 cm in both groups.

Patients with carcinoma of the lower third of the rectum who require very low anterior resection with total mesorectal excision are better served with total rectal excision, construction of a colonic pouch and anastomosis of the pouch to the anus or anorectal junction, rather than joining the colon to an ischaemic rectal stump.

F. Seow-Choen

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1. Nicholls RJ, Lubowski DZ, Donaldson DR. Comparison of colonic reservoir and straight colo-anal reconstruction after rectal excision *Br J Surg* 1988, **75**. 318–20.
2. Seow-Choen F. Controversies in colorectal surgery· colonic pouch after very low anterior resection for carcinoma of the distal third of the rectum *Ann Acad Med* 1993 (in press).

Authors' reply

Sir

We are grateful for the interest shown by Mr Seow-Choen in our paper, which looked at function of the distal rectum after low anterior resection for carcinoma.

He has correctly pointed out that while there was only one leak in 27 patients when the anastomosis was 3 cm from the anal verge, there were five leaks in 56 when the anastomosis was 6 cm from the anal verge Contrary to his observations, however, there is in fact no statistically significant difference in these leak rates ($P=0.65$, Fisher's exact test), so we were reluctant to draw any conclusions from this difference.

We are, however, very interested in the excellent functional results Mr Seow-Choen has obtained after total rectectomy with total mesorectal excision using the colonic pouch for reconstruction. Although his study has only 19 patients in two groups (colonic pouch–anal *versus* straight coloanal anastomoses), the early results for the colonic pouch–anal group appear promising. Our experience has also been that the few colonic pouch procedures we have performed have produced excellent functional results Long-term studies with larger numbers will eventually determine the best form of reconstruction after total rectectomy with total mesorectal excision for lesions of the lower third of the rectum.

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R. J. Heald

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Primary papillary carcinoma of a thyroglossal duct cyst: report of a case and literature review

Sir

We were interested in the article by Weiss and Orlich (*Br J Surg* 1991, **78**· 87–9), having ourselves recently excised a primary papillary carcinoma within a thyroglossal cyst The patient was a 66-year-old man who presented with a lump in the neck that had been present for 10 years He was asymptomatic but had sought advice because the lump had recently increased in size Examination revealed a 3 × 3 cm firm midline swelling between the thyroid cartilage and hyoid that was not tender and did not transilluminate but moved cranially on protrusion of the tongue. The thyroid gland was clinically normal and there was no cervical lymphadenopathy. Ultrasonography of the neck confirmed a 3-cm cystic lesion separate from the thyroid gland. Technetium scanning demonstrated normal thyroid uptake and distribution with no evidence of pyramidal lobe activity Thyroid function test results were normal

At elective operation the cyst was situated between the alae of the thyroid cartilage and fixed between the body of the hyoid and the thyroid cartilage, with the thyroglossal duct passing through the hyoid bone. The thyroid gland was macroscopically normal. A Sistrunk procedure was performed, and the patient made an uncomplicated recovery Pathological examination showed a 5-mm papillary growth within the lumen of the cyst Microscopic examination confirmed a thyroid papillary carcinoma and the presence of psammoma bodies There was no evidence of invasion or lymphatic permeation. Follow-up thyroid function tests, computed tomography of the neck and isotope scanning revealed no further abnormalities. The patient was commenced on thyroxine to suppress thyroid-stimulating hormone (TSH), and no further surgery has been considered necessary.

While agreeing with the authors that primary papillary carcinoma with no detectable metastases should be treated by a Sistrunk procedure without thyroidectomy, we would also advocate postoperative thyroxine administration We believe that this is a sensible precaution, since papillary carcinoma of the thyroid gland is TSH dependent and it would be expected that a papillary carcinoma of a thyroglossal cyst would share this characteristic.

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Pylorus-preserving *versus* standard pancreaticoduodenectomy: an analysis of 110 pancreatic and periampullary carcinomas

Sir

The British Journal of Surgery has repeatedly emphasized the importance of reliable statistical methods. However, this does not relieve the reader from critical judgement The paper of Roder and colleagues (*Br J Surg* 1992, 79: 152–5) shows how strong conclusions can inappropriately be drawn from deficient statistical analysis

By using the word '*versus*' in the title the paper appears to be a controlled study, but it is not Only the scrupulous reader may notice that the decision to perform either of two surgical procedures 'was made according to the *preference* (my italics) of the senior surgeon performing the operation', introducing an insuperable bias. Furthermore, many co-factors to the survival (i.e tumour stage and grade) are disregarded simply by creating so many subgroups that the resulting small numbers are unable to establish any statistical significance. In this way a series of type II errors conceals what is actually missing a multivariate analysis.

I feel there is a great chance that the interpretation of the results of this otherwise impressive series of pancreatic resections could be entirely different from that reported. Therefore, I strongly recommend the authors to subject their survival data to a multiple regression analysis using the Cox proportional hazards model

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Authors' reply

Sir

We appreciate Dr Blankensteijn's comments on our paper and thank you for the chance to address his concerns As Voltaire said: 'The best is the enemy of the good'. As clearly stated in the *Patients and methods* section, our study was a retrospective analysis of data collected prospectively according to a standardized protocol. Of course we agree with Dr Blankensteijn that a randomized prospective trial comparing standard and pylorus-preserving pancreaticoduodenectomy would be the ultimate way to establish the superiority of one or other procedure. Because of the low number of patients undergoing resection in individual centres such a study has not so far been performed and probably never will be. We therefore feel that the results of our relatively large albeit retrospective series from a single centre merit publication because the findings are useful to establish new hypotheses.

The distribution of tumour stage and grading in our patient population was shown in *Table 1* and did not differ significantly between the two treatment groups. Our analysis, however, clearly demonstrated a superiority of standard pancreaticoduodenectomy, particularly in patients with stage III cancer of the head of the pancreas. According to Union Internacional Contra la Cancrum guidelines, tumour stage constitutes the strongest factor influencing survival. Since our analysis showed a significant difference in survival between the two procedures at various stages of the disease, a type II error could not occur

It can be useful (and is certainly trendy) to perform multivariate stepwise regression analysis to identify prognostic factors. However, the low number of patients in the present and all other studies precluded an intelligent application of this statistical tool In fact, the limited number of cases in individual centres frequently does not allow separate analysis of even such different entities as pancreatic and periampullary carcinoma In our opinion a meta-analysis of published data on the two procedures followed by a prospective randomized study would be the best way to clarify the issues We are eagerly awaiting the results of such a study with multivariate analysis from Dr Blankensteijn. For the time being, standard pancreaticoduodenectomy with distal gastric resection remains the procedure of choice at our institution for resection of carcinoma of the head of the pancreas.

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Dual publication – again

Sir

I noted again your difficulties with dual publication highlighted in the July issue (*Br J Surg* 1992, 79: 601) and your attempts to contact the principal authors. While spot checks and sanctions may help, I fear the problem is a symptom of a more serious malaise afflicting surgery (and medicine) in general.

The authors concerned in these episodes are victims of the crushing pressure placed on trainees to 'publish or perish' Trainees feel that publications, especially in a prestige journal, are the only overt yardstick used in deciding senior registrar appointments. Thus the pressure to maximize output during the period of full-time research, and hence dual publication, 'salami slicing' and 'data manipulation'.

While departments vary in strictness, some of the responsibility for this malaise must rest with the supervisors of these research projects. Ultimately the fault is generated by a system of advancement based almost quantitatively on publications to the exclusion of other factors. Until the profession as a whole addresses these attitudinal problems and resolves them sensibly, some form of 'publication-stretching' will always exist.

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Book reviews

Bailey and Love's Short Practice of Surgery. 21st ed.

C. V Mann and R C G. Russell (eds). 250 × 170 mm. Pp 1519 Illustrated. 1992. London Chapman and Hall £49

Bailey and Love celebrates its 60th anniversary with a 21st edition, a new editorial team and a change of publisher. The latest edition also sees a considerable change in the list of specialist contributors, now totalling 37 internationally recognized authorities. Despite these changes, the structure, presentation and much of the text remain familiar, indeed large tracts are unaltered from my own 15-year-old 17th edition.

The stated target readership of the book is both senior students and surgeons in training. It aims to provide these two disparate groups with the essential facts that form the basis of sound clinical judgement and are necessary to achieve a satisfactory outcome in their respective examinations. Laudable though these objectives are, can a single text really meet their particular requirements? The crowded undergraduate curriculum militates against the use of this type of publication as a basic learning tool. As a reference work the absence of either a bibliography or source references is a serious disadvantage to the student What of prospective Fellowship candidates: does this book come any nearer to meeting their needs? Unfortunately, sole reliance on this text is unlikely to result in the desired outcome The developing edges of surgery often receive too little discussion and too much of the text is littered with dogma. Woe betide the candidate who faces the topical question of current management options in cholelithiasis who is depending on this text alone – laparoscopic cholecystectomy is accorded four lines of small print.

Despite these problems *Bailey and Love* will undoubtedly remain a popular and successful publication. Its strength lies in the presentation of clinical detail all so easily ignored in this technological age. Testimony to its continued popularity is that our medical school library has already obtained six copies of the 21st edition and none of these was to be found on the shelves today, albeit in the week before Finals!

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Practical Guide to Surgical Pathology with Cytologic Correlation. A Text and Color Atlas

K. Kim and B Naylor. 286 × 219 mm Pp.359. Illustrated 1992 New York: Springer-Verlag.

My initial impression of this book was rather favourable in that it was attractively laid out and pleasant to handle, being of a convenient size On closer examination, however, I was disappointed by the frequently inferior quality of the photomicrographs. Many have an overall blue cast that frequently obscures detail. In addition, in many of the low-power pictures, the condenser appears not to have been centred and there is a marked gradation in the intensity of the background illumination In a book dedicated to histopathological and cytopathological interpretation the authors should have been more critical in their selection of illustrations. The authors cover all systems and of necessity this results in limiting the number of figures related to each condition. Consequently, important features cannot be illustrated. This severely limits the utility of the book since it would be an inadequate reference source for a practising cytologist or histopathologist, who would almost certainly refer to larger and more definitive texts. The authors' hope that the book will prove useful to practising pathologists as a quick reference is, I think, overambitious. The success of this book depends on its appeal to non-specialists, I cannot help feeling that there are many alternative publications already available to satisfy this need

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Coloproctology and the Pelvic Floor. 2nd ed.

M. M Henry and M Swash (eds) 250 × 195 mm. Pp.499 Illustrated 1992. Oxford Butterworth–Heinemann £95

It was indeed a pleasure to review this superb book which is at the same time scholarly and practical It represents an extensive revision and expansion of the material contained in the first edition, and the editors have assembled an impressive array of international experts to produce a volume in which the consistently high standard and minimal repetition presumably reflects tight but sensitive editorial control. The contents are divided into four sections. The first deals with the anatomy and physiology of the rectum and pelvic floor and, if any chapter is to be singled out, it would be that by Duthie and Bartolo which succinctly elucidates current understanding of faecal continence and defaecation In the second section, investigation of pelvic floor disorders is covered and there is a welcome emphasis on the clinical significance of anorectal physiology The third section is concerned mainly with the treatment of pelvic floor disorders; the difficult problems of incontinence and constipation are given thorough coverage and there are useful chapters on solitary rectal ulcer, prolapse, urinary incontinence, fissures and haemorrhoids In the last section there are six short but excellent essays on 'other problems'

It is perhaps a little disappointing that the editors have not seen fit to include fistula *in ano* in their otherwise comprehensive and authoritative book, but this is a minor quibble. Any surgeon whose practice embraces coloproctology will find this book to be an invaluable companion when faced with problems related to the pelvic floor. It should be regarded as mandatory reading by all involved in this challenging field.

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Technologies in Vascular Surgery

J S T Yao and W. H. Pearce (eds). 265 × 187 mm. Pp.525 Illustrated. 1992. Philadelphia: W. B. Saunders. £87.

Vascular surgery is still expanding and this is to some extent a function of the synchronous developments in technology off which it has fed Some of the latter, such as nuclear magnetic resonance techniques, have developed fortuitously. Others, like colour duplex scanning, have principally been demand led by the speciality itself Thus the discipline has become increasingly and perhaps uniquely 'technically orientated', and it is not therefore surprising to have seen such a proliferation of vascular textbooks in the past few years. This has led to considerable and inevitable duplication Is this true of *Technologies in Vascular Surgery*? This is the latest annual volume from the stable of Dr Jimmy Yao with a new partner, Dr William Pearce, and emanates from the annual symposium held in Chicago in December of each year. There are 105 contributions from leaders in their various fields, almost exclusively from North America. The title leaves plenty of room for topics and these cover basic investigations, and aspects of treatment and postoperative care, both immediate and long term. It addresses new developments in established procedures, the growing edge of management, and some considerations that are clearly more theoretical and for the future, such as genetic engineering Apart from this, basic concepts such as diagnostic radiology, intravascular procedures and other interventional techniques are discussed comprehensively.

Because so many of these areas are changing rapidly, there is room for a constant update This book admirably and comprehensively fulfils this role. The chapters are authoritatively written and extensively researched and referenced. This is an invaluable book for any practitioner of the art and science of vascular surgery, as a source of general reading and information, and for reference purposes.

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Atlas of Venous Surgery

J. J. Bergan and R. L. Kistner (eds). 285 × 220 mm. Pp. 285. Illustrated. 1992. Philadelphia: W. B. Saunders. £54.

Despite the rich flow of vascular publications in recent years there has, until now, been a substantial gap. Compared with arterial surgery there is much less conformity or certainty as to the appropriate surgical treatment of venous disorders. Bergan and Kistner have brought together an outstanding group of authors to discuss the management of the full range of venous disorders from spider naevus to venous thrombosis.

Conservative management, especially important in venous disease, is not neglected. In respect of surgical techniques, sections of particular interest are the description by O'Donnell of the techniques for dealing with incompetent perforating veins, ranging from the classical long medial incision (Linton/Cockett) to video-controlled endoscopic division. Many will be interested to read Goldman's chapter on the sclerotherapy of varicose and spider leg veins. Scurr describes the Psathakis procedure for deep vein incompetence, Greenfield provides an update on techniques for filter insertion. Techniques for valve reconstruction, replacement or transposition are described by Kistner, Raju and Sottiurai.

The practical details in the text and the line drawings are clear enough to guide anyone wishing to undertake these difficult areas of surgery. Surely the time is long overdue for more vascular surgeons to specialize in venous disorders. For anyone wishing to do so, this book is invaluable.

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Baillères's Clinical Gastroenterology: International Practice and Research – Anorectal Disorders

M. M. Henry (ed.) 232 × 150 mm. Pp. 218. Illustrated. 1992. London: Baillière Tindall. £27·50.

This book reflects the standing of its editor, whose eminence in this field has allowed him easily to bridge the cultural divides between the UK, Europe, USA, South America and the antipodes, and obtain contributions from each of these places. This non-specialist reviewer learned much from the book and the advice was generally consistent where articles overlapped: anorectal physiology measurements, while helpful in incontinence, are not so useful in constipation; ileal pouch–anal anastomoses are not the answer for all those with chronic ulcerative colitis; and the ill-understood internal anal sphincter demonstrates abnormality in function in many anorectal diseases.

I found it strange to read the preface apologetically explaining the need to include colonic topics to ensure a wider range of readership. This book's strength is in the authoritative nature of its articles on the anorectal topic. The review articles on non-anorectal topics such as familial polyposis coli and the nutritional aspects of inflammatory disease of the rectum lie strangely awry and, in fact, detract from more powerful articles that are related to the title of this review. Do read the book though: more than two-thirds of it is a fine review of progress in this only recently investigated area.

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Notices and announcements

11 December 1992

Role of the Plain Abdominal Radiograph in the Acute Abdomen

Canterbury, UK

Information· Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

3–6 January 1993

Postgraduate Course in Gastroenterology

Oxford, UK

Information Dr D. P Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

7–8 January 1993

Surgical Research Society Meeting

London, UK

Information Professor J R Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

16–17 January 1993

Hong Kong Surgical Forum – Winter 1993

Hong Kong

Information Alice Iu, Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

5 February 1993

Transjugular Intrahepatic Portocaval Shunts

Toulouse, France

Information Service d'Hépato-Gastro-Entérologie, CHU Purpan, 31059 Toulouse, France

8–10 February 1993

Child Safety in Southern Africa

Cape Town, South Africa

Information Deborah McTeer, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape, South Africa

18–20 February 1993

Colorectal Disease in 1993: an International Exchange of Medical and Surgical Concepts

Fort Lauderdale, Florida, USA

Information The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Room TT-31, Cleveland, Ohio 44195-5241, USA

21 February 1993

Phlebology Review

Lake Buena Vista, Florida, USA

Information· North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, California 92024, USA

22–24 February 1993

Sixth Annual Congress of the North American Society of Phlebology on the Advances in Sclerotherapy and the Advances in Surgical and Medical Treatment of Venous Disease

Lake Buena Vista, Florida, USA

Information. North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, CA 92024, USA

5–7 March 1993

Impact of HIV Infection on the Gastrointestinal Tract

Bologna, Italy

Information Noema Congressi, Via Lame 24, 40122 Bologna, Italy

12–15 March 1993

7th Congress of the Western Pacific Association of Critical Care Medicine

Hong Kong

Information Ms E. Lindsay, Secretariat, International Conference Consultants Ltd, Suite A/B, 16 F, Casey Building, 38 Lok Ku Road, Sheung Wan, Hong Kong

19–20 March 1993

2nd European Congress on Ambulatory Surgery

Brussels, Belgium

Information Dr Cl De Lathouwer, Brussels One Day Clinic, Nouvelle Clinique de la Basilique, 37–47 Rue Pangaert, B-1080 Brussels, Belgium

31 March–2 April 1993

UICC Kyoto International Symposium on Recent Advances in Management of Digestive Cancers

Kyoto, Japan

Information Professor T Takahashi, Department of Surgery, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602, Japan

14–16 April 1993

Association of Surgeons of Great Britain and Ireland Annual Meeting

Birmingham, UK

Information Caroline Ross, Association of Surgeons of Great Britain and Ireland, at The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

7–8 June 1993

8th International Symposium – Applied Physiology in Clinical Respiratory Care

Rotterdam, The Netherlands

Information Dr O Prakash, Thorax Centre BD 164, Dijkzigt Hospital, Dr Molewaterplein 40, 3015 Rotterdam, The Netherlands

8–11 June 1993

World Association of HPB Surgery 1st European Congress of Surgery

Paris, France

Information EHPBS Congress Secretariat, Congress House, 65 West Drive, Cheam, Surrey SM2 7NB, UK

9–12 June 1993

The Endocrine Society 75th Annual Meeting

Las Vegas, Nevada, USA

Information Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

5–8 July 1993

First International and Eighth European Conference on Clinical Hemorheology

Vienna, Austria

Information Professor E. Ernst, Department of Physical and Medical Rehabilitation, University of Vienna, AKH Währinger Gurtel 18–20, 1097 Vienna, Austria

6–17 July 1993

Current Practice in Neonatal and Paediatric Surgery

Manchester, UK

Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

8–9 July 1993

Surgical Research Society Meeting

Dundee, UK

Information· Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

8–10 July 1993

5th Southeast European Symposium of Paediatric Surgery

Graz, Austria

Information Professor M. E. Hollwarth, Department of Paediatric Surgery, University of Graz, Heinrichstraße 31, A-8010 Graz, Austria

19–24 July 1993

Second United European Gastroenterology Week

Barcelona, Spain

Information Professor J R Malagelada, Calle Calvet 55–57, 08021 Barcelona, Spain

22–28 August 1993

35th World Congress of Surgery of the International Society of Surgery

Hong Kong

Information Scientific Secretariat, c/o ISS/SIC, Hauptstraße 63, PO Box 411, CH-4153, Reinach BL 1, Switzerland

15–18 September 1993

Eurosurgery '93

London, UK

Information. Professor J P S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

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OCTOBER 1992/VOLUME 164/NUMBER 4

SCIENTIFIC PAPERS

311 Summary of Pancreas Club Meeting

The important papers presented at the May 9, 1992, meeting of this group with a special interest in the pancreas are summarized herein.

316 Management of Small Artery Vascular Trauma
Jeffrey L. Ballard, T. J. Bunt, and James M. Malone

The results of an 11-year retrospective study involving 99 arterial injuries distal to the brachial bifurcation or popliteal trifurcation in 88 patients are described. If there is one uninjured patent infrabrachial or infrapopliteal vessel, then the remaining vessel(s) may be either repaired or ligated. Nerve injury is the single most important aspect of extremity trauma in terms of function loss and long-term outcome.

320 Lower-Extremity Amputation With Immediate Postoperative Prosthetic Placement
David Folsom, Terry King, and Jeffrey R. Rubin

A retrospective review of 65 patients undergoing 69 major lower-extremity amputations with immediate postoperative prosthesis was performed. Successful rehabilitation was achieved in 86% of patients with an average time interval from operation to independent ambulation of 15.2 days in below-knee amputees and 9.3 days in above-knee amputees.

323 Prognostic Significance of Co-Expression of c-*erb*B-2 Oncoprotein and Epidermal Growth Factor Receptor in Breast Cancer Patients
Akihiko Osaki, Masakazu Toi, Hirofumi Yamada, Hiroyuki Kawami, Katsumasa Kuroi, and Tetsuya Toge

In 115 patients with primary breast cancer, the expression of c-*erb*B-2 oncoprotein and epidermal growth factor receptor (EGFR) was investigated by immunocytochemical assay and biochemical competitive binding assay, respectively. Clinical survey demonstrated that c-*erb*B-2 oncoprotein and EGFR expression each have independent prognostic values and, when the patients were stratified into three groups on the basis of their status for both factors, those who were doubly positive for c-*erb*B-2 oncoprotein and EGFR had a worse prognosis than other groups. The authers conclude that the combination of the expression of c-*erb*B-2 oncoprotein and EGFR may be important in selecting those patients with a poor prognosis.

327 Gastric Antroplasty for the Treatment of Delayed Gastric Emptying and Gastroesophageal Reflux in Children
Eric W. Fonkalsrud, Marvin E. Ament, and Jorge Vargas

Vertical incision of the antral muscularis without mucosa (antroplasty) is a helpful, simple adjunct to fundoplication in children with symptomatic reflux and delayed gastric emptying. Antroplasty performed in 56 children produced equally good results as Heineke-Mikulicz pyloroplasty in 59 children and had very low morbidity.

332 Nissen Fundoplication in the Treatment of Children With Familial Dysautonomia
Raphael Udassin, Dan Seror, Itzhak Vinograd, Oded Zamir, Simon Godfrey, and Shemuel Nissan

Thirty-four children with familial dysautonomia (FD) who underwent Nissen fundoplication and gastrostomy showed significant improvement at long-term follow-up. There was cessation of vomiting, improved pulmonary function, improved nutrition and hydration, and less frequent hospital admissions. These long-term results coupled with the absence of operative mortality and the low postoperative morbidity should encourage early surgical intervention in selected FD patients.

337 Further Evidence Against the Routine Use of Parathyroid Ultrasonography Prior to Initial Neck Exploration for Hyperparathyroidism
Per-Olof Hasselgren and James P. Fidler

Preoperative parathyroid ultrasonography in 46 consecutive patients undergoing initial neck exploration for hyperparathyroidism had low sensitivity (54%) and accuracy (70%) and a high rate of false-negative results (46%), suggesting that there is no role for the routine use of ultrasonography in patients undergoing initial neck exploration for hypercalcemia.

341 Lipocortin-Present Perforating and Lipocortin-Absent Nonperforating Crohn's Disease
Youichirou Sakanoue, Takao Horai, Tomoaki Okamoto, Takuya Hatada, Yasutsugu Shoji, Shinsuke Fujita, Masato Kusunoki, and Joji Utsunomiya

To determine whether there are two different clinical forms of Crohn's disease, the concentrations of lipocortin and prostaglandin E_2 in the inflamed mucosa of 12 patients with strictly controlled Crohn's disease were compared with those found in histologically normal mucosa from normal control subjects. The results indicate that there may be two distinct patterns of Crohn's disease in which the amount of lipocortin varies.

345 Long-Term Follow-Up of Partial Splenectomy in Gaucher's Disease
Ian J. Cohen, Kalman Katz, Enrique Freud, Michael Zer, and Rina Zaizov

Long-term follow-up of seven children who underwent partial splenectomy for Gaucher's disease is presented. No bone crises occurred in the five patients who were without previous crises. In all patients, hypersplenism recurred, and total splenectomy was required 3 to 8 years later in three patients.

348 Treatment of Adenocarcinoma of the Pancreas With Somatostatin and Gonadoliberin (Luteinizing Hormone-Releasing Hormone)
The French Associations for Surgical Research, Michel Huguier, Guy Samama, Jacques Testart, Serge Mauban, Abe Fingerhut, Jean Nassar, Sidney Houry, Daniel Jaeck, Philippe De Mestier, Jean Pierre Favre, Francis Michot, Alain Vidrequin, Georges Mantion, Michel Veyrières, Gilles Fourtanier, Patrice Lointier, and Marc Gignoux

This randomized study compared the potential value of three hormonal therapy regimens in a study group of 163 patients with adenocarcinoma of the pancreas who did not undergo resection for cure. The mean survival times were 6 months in the luteinizing hormone-releasing hormone (LH-RH) plus somatostatin group, 5.5 months in the LH-RH group, 4.3 months in the control group, and 3.8 months in the somatostatin group. However, the life-table analyses for all randomized patients, and separately according to sex, the lymph node extension, and metastatic spread, were not different between groups.

354 Collagen Synthetic Capacity Throughout the Uninjured and Anastomosed Intestinal Wall
Michael F. W. C. Martens, Ben M. de Man, Thijs Hendriks, and R. Jan A. Goris

Collagen synthetic capacity was measured throughout the uninjured and anastomosed intestine of the rat. Significant differences were found between different sites. The increase after anastomotic construction is not restricted to the wound site but represents a more generalized response.

PETER OLCH MEMORIAL LECTURE

361 Samuel Preston Moore: Surgeon-General of the Confederacy
Peter N. Purcell and Robert P. Hummel, Jr.

Samuel Preston Moore, Surgeon-General of the Confederate States Medical Department, was responsible for many innovations during his command. He transformed the medical corps from a mediocre collection of surgeons into a highly effective department that performed thousands of procedures on and off the battlefield and saved the lives of many soldiers during America's bloodiest war.

HOW I DO IT

366 Abdominoinguinal Incision in Resection of Pelvic Tumors With Lateral Fixation
Constantine P. Karakousis

Pelvic tumors with lateral fixation have often been considered unresectable through conventional abdominal incisions, or they have been treated with hindquarter amputation. The abdominoinguinal incision provides the necessary exposure that makes resectable the majority of these tumors with preservation of the extremity.

ASSOCIATION FOR SURGICAL EDUCATION

372 Utility of an Oral Examination in a Surgical Clerkship
James Hassett, Fred Luchette, Ralph Doerr, George Bernstein, John Ricotta, Nicholas Petrelli, Jaroslaw Stulc, G. Richard Curl, Frank McI. Booth, and Eddie Hoover

This report of a prospective and randomized study of the oral examination in a surgical clerkship identifies its usefulness in student assessment. It may be a valuable tool for student feedback, professional development, career advisement, and graduate training recommendations. It does not discriminate between groups of students with average or low levels of cognitive competence.

377 Composite Resident Work Week
Sidney F. Miller

An analysis of resident work hours as reported on time cards reveals that the average hours worked ranged from 60 to 83 hours. Patient rounds, time scrubbed, and on-call hours accounted for the majority of the resident's time. The uniqueness of the individual program, actual activities, and total hours must be considered when dealing with this issue.

BRIEF REPORT

382 Complications and Diagnosis of Meckel's Diverticulum in 776 Patients
Hiroki Kusumoto, Motofumi Yoshida, Ikuo Takahashi, Hideaki Anai, Yoshihiko Maehara, and Keizo Sugimachi

Based on data from 776 Japanese patients, the authors conclude that, in the case of complications of intestinal bleeding, technetium 99m-pertechnetate scintigraphy will lead to an accurate diagnosis. In acute cases, a combination of imaging procedures is useful.

REVIEW

384 Intestinal Obstruction Complicating Pregnancy
Philip W. Perdue, Harry W. Johnson, Jr., and Perry W. Stafford

A retrospective review of 66 cases of intestinal obstruction complicating pregnancy was performed. The most common causes of obstruction were adhesions, volvulus, and intussusception. Maternal mortality was 6%, and fetal mortality was 26%.

MOLECULAR BIOLOGY

389 Molecular Mechanisms of Tumor Formation
Ghassan Samara, Michael Hurwitz, Mark Sawicki, and Edward Passaro, Jr.

The alterations in DNA that can lead to abnormal or absent proteins and the role of chromosomal alterations in changing the function of the DNA are reviewed. The role of viruses in derailing a cell's normal functions, the major mechanisms of oncogene action, and tumor suppressor genes are also discussed.

397 Letters to the Editor

401 Book Reviews

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

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The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988, **108** 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

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Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

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These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

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methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

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Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

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The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points

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References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$ References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example. De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications.* New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

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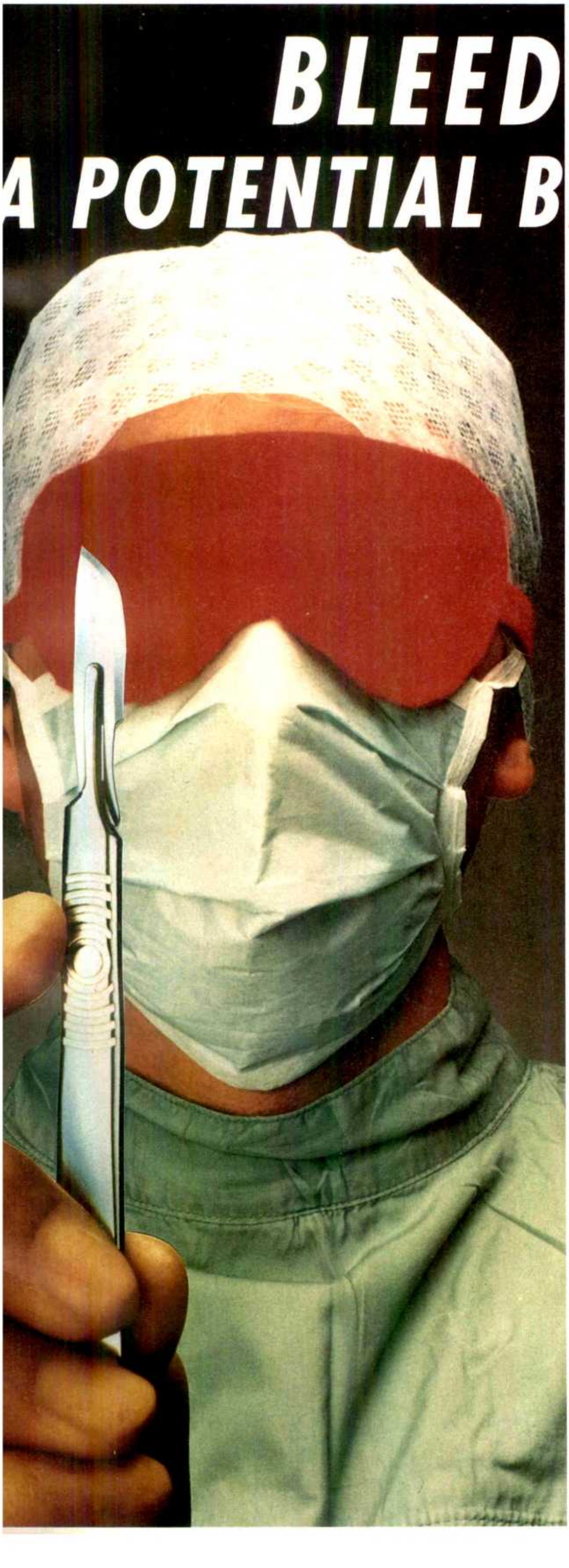

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In conclusion it was suggested th patients should be told of the options availab and have the decisive word about which form treatment to be chosen.

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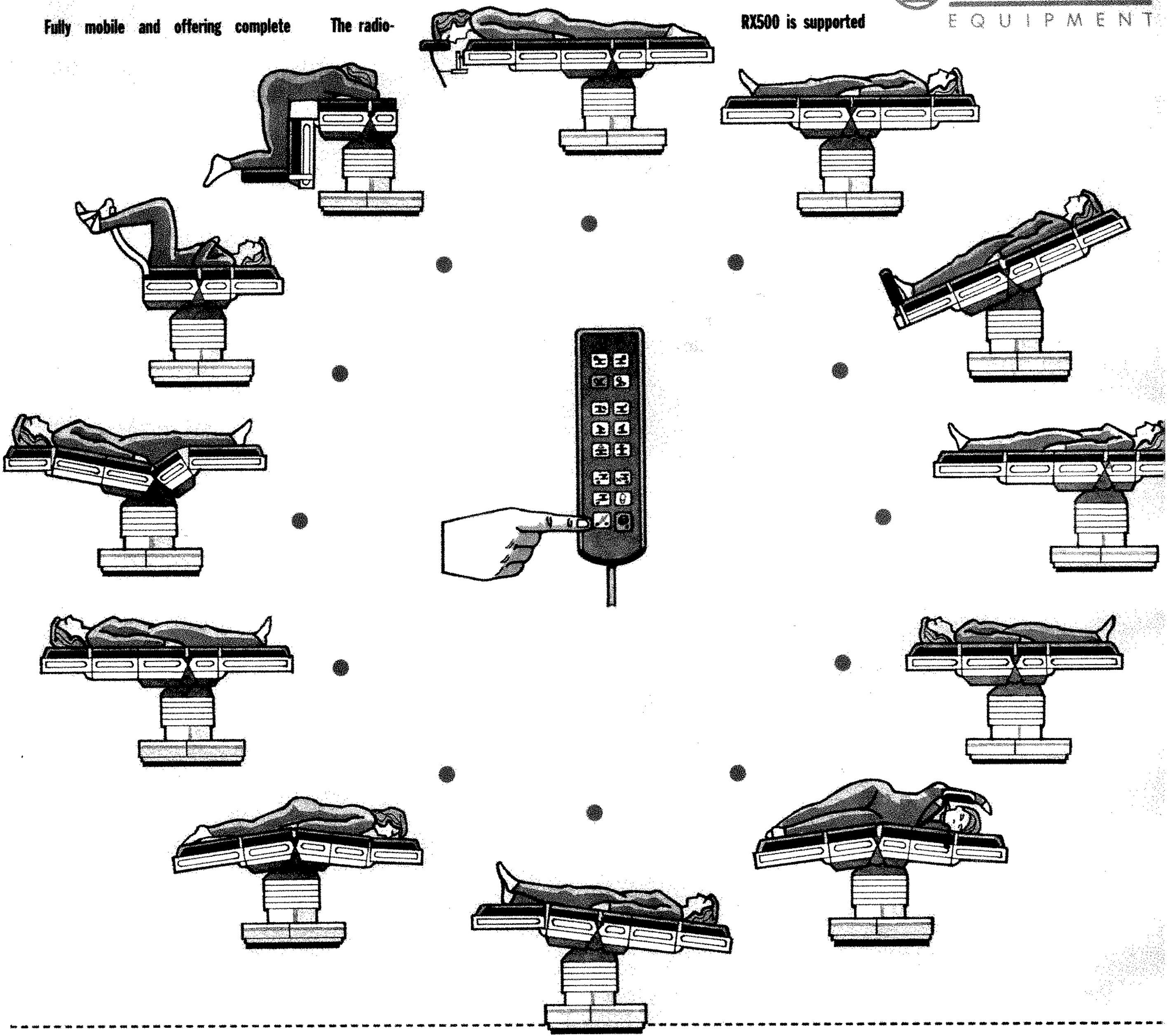

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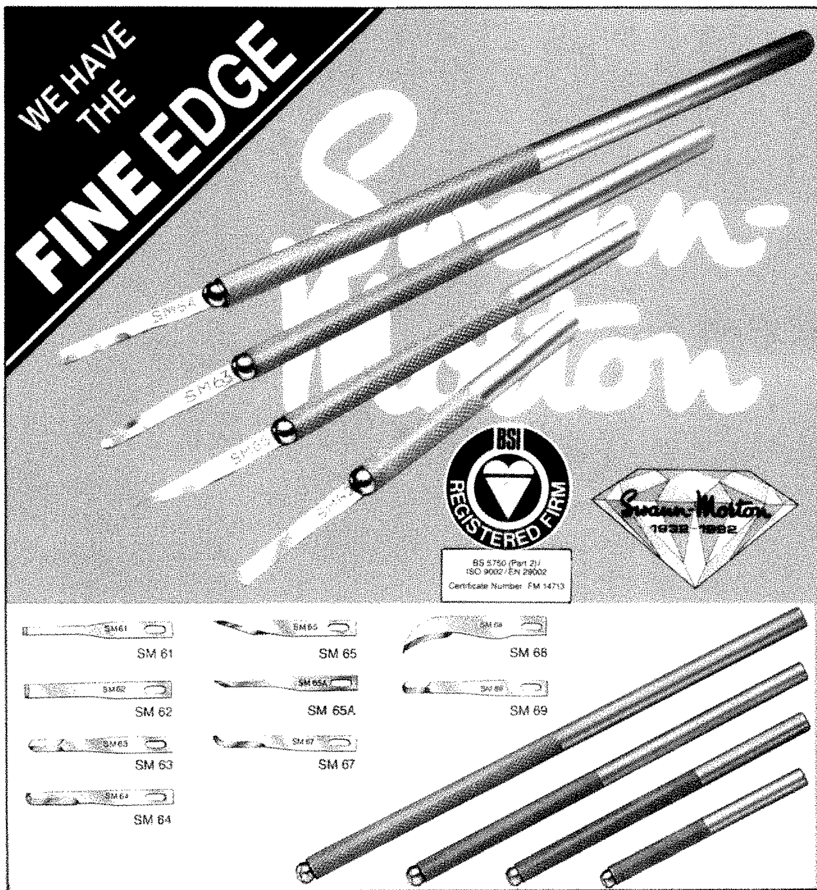

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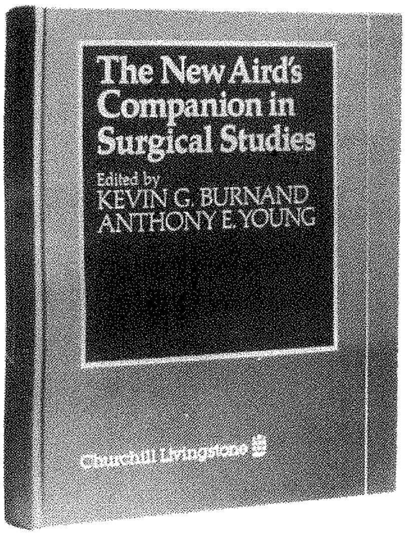

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Br. J. Surg. 1992, Vol. 79, December, 1257

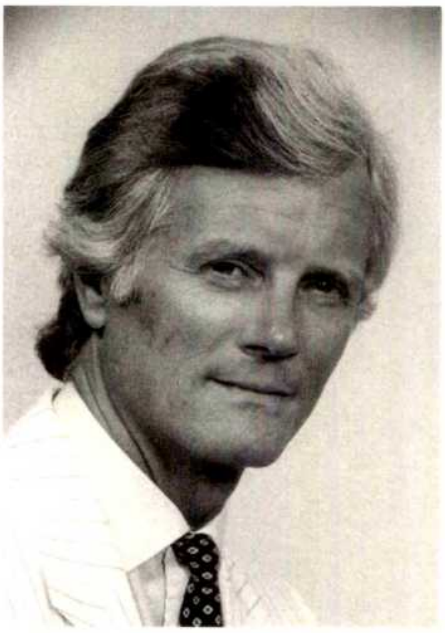
Continuing our profiles of Members of the Board from the British Isles.

PROFESSOR DAVID LLOYD

David Allden Lloyd (born 1940) is Professor of Paediatric Surgery at Liverpool. He was born and educated in South Africa, came to medical school in England (Cambridge and Bart's) and reached his present position via consultant/staff posts in Ladysmith (South Africa) and Pittsburgh (USA). Within paediatric surgery his interests include trauma, oncology and metabolism of the neonate with particular reference to parenteral nutrition and the effects of surgical stress. He holds the Fellowships of surgical colleges in England, South Africa, Canada and the USA.

MR DAVID TWEEDLE

David Ernest Frederick Tweedle (born 1940) is a consultant surgeon at the University Hospital of South Manchester. He qualified from St Andrew's University and his training included appointments in Newcastle upon Tyne and Boston, USA. In 1971 he obtained the Moynihan Medal for work on post-operative energy expenditure. He is former Treasurer of the Surgical Research Society and a current examiner for the Edinburgh College of Surgeons. His particular interests are in pancreatic and hepatobiliary surgery.



MR STEPHEN LEVESON

Stephen Leveson (born 1946) is a consultant surgeon at York. He qualified at the University of Manchester and trained at Leeds, with 1 year as a research associate at Roswell Park Memorial Institute, Buffalo, New York, USA. He was appointed a senior lecturer at St James's Hospital, Leeds, in 1980 and took up his present position in 1985. He is a surgical oncologist with particular interests in colorectal carcinogenesis and liver blood flow in metastatic disease.

Robin Williamson

Editor's note: October's profile of Professor Cristobal Pera incorrectly described him as having trained in Valladolid; this should have been Santander. Apologies to Professor Pera for this mistake.

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Br. J. Surg. 1992, Vol. 79, December, 1258–1259

Aprotinin therapy and blood conservation: extending the indications

Blood conservation is now acknowledged as a priority in all forms of major surgery. Professional and public awareness of the risks associated with the use of homologous blood or blood product transfusions have risen sharply in recent years. Two different but complementary approaches to blood conservation have emerged: autotransfusion and the use of pharmacological agents to reduce peroperative bleeding.

The pharmacological approach is conceptually more attractive because it aims at prevention, or at least reduction, of the primary bleeding. Until recently, however, the drugs that had been used (including epsilon aminocaproic acid, prostacyclin, desmopressin and dipyridamole)[1–3] failed to exhibit significant or consistent efficacy and made little or no impact on blood transfusion requirements, particularly in high-risk patients. The serendipitous discovery of the blood-sparing role of high-dose aprotinin (Trasylol; Bayer, Newbury, UK) in patients undergoing cardiac surgery[4] has changed this. For the first time, a pharmacological agent has been truly effective in reducing peroperative bleeding and the need for blood and blood product transfusion. This high degree of efficacy has been demonstrated not only in routine primary cases but also in repeat operations, in patients with coagulation disorders and in those with active sepsis from uncontrolled infective endocarditis. The results from initial single-centre reports have been confirmed in large multicentre studies[5]. Clinical use of aprotinin is now widespread in cardiac surgical practice in several European countries and prelicensing studies in North America will soon be completed.

The question to be considered now is obvious: 'Is aprotinin therapy similarly effective in reducing blood loss in other types of major surgery?' It cannot be assumed that efficacy will be similar because cardiac surgery is a unique surgical scenario related to the obligatory use of cardiopulmonary bypass. Cardiopulmonary bypass is associated with a complicated pathophysiology that includes several significant haematological and haemostatic side-effects not considered to be features of non-cardiac procedures. In addition to mandatory systemic heparinization, the contact activation process (where the patient's circulating blood passes over the artificial surfaces of the extracorporeal circuit) induces a series of haematological reactions including both fibrinolysis and kallikrein and complement activation[6]. Disturbances in platelet function and reductions in platelet surface receptor populations are also described during bypass. Although the precise mode of action of aprotinin therapy in cardiac surgery remains unclear, many believe that the inhibition of increased fibrinolysis (a known effect of a serine protease inhibitor such as aprotinin) is the principal mode of action. If this is so, then aprotinin therapy in non-cardiac procedures might be expected to reduce peroperative bleeding only if increased fibrinolysis were a feature of such surgery. These possibilities are obviously intriguing and require proper study. Urological surgery for example, with its associated urokinase-producing epithelium, seems a logical area to investigate.

In fact, despite the lack of such scientific evidence, there are already empirical data showing that aprotinin therapy does have a similar efficacy in reducing bleeding in non-cardiac procedures. A preliminary report from Thompson *et al.*[7] has described significant reductions in blood loss both during and after aortoiliac surgery. From studies of hepatic surgery, Mallett *et al.*[8] reported similar efficacy in reducing blood loss, particularly during the anhepatic phase of liver transplantation. This particular finding is interesting because the anhepatic phase is associated with a hyperfibrinolytic state. For pulmonary surgery, Cooper[9] recently reported significant reductions in peroperative blood loss and transfusion requirements in patients undergoing bilateral lung transplantation for cystic fibrosis. There are also anecdotal reports of the use of aprotinin therapy in surgery for arteriovenous malformations.

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Such preliminary clinical data suggest that aprotinin therapy will be shown to be effective in reducing bleeding in non-cardiac procedures and that it will have a significant role in blood conservation in surgery in general. At this point, however, a word of caution is necessary. Before aprotinin is grasped eagerly as the answer to bleeding problems in all surgical procedures, the same degree of thought must go into dosage levels, and the same care must be exercised in carrying out prospective placebo-controlled trials as in the initial cardiac surgery studies. Only then will the very real potential for extending the indications of this powerful drug be fully and safely realized.

K. M. Taylor

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Endoscopic treatment for chronic pancreatitis

Endoscopic biliary stenting is an accepted alternative to surgical decompression of the obstructed bile duct, but interventional endoscopic procedures on the pancreatic duct are still in their infancy. The role of therapeutic endoscopy in the management of pancreatic disease remains speculative, despite technical progress and an increasing experience in some centres. Progress is largely the result of the development of wide-channel endoscopes that allow better manipulation and the placement of larger diameter stents. The ability to drain a duct system or a cyst raises the question of whether such drainage procedures have a role in the clinical management of chronic pancreatitis. Before endoscopic drainage is undertaken, it is axiomatic that a surgical decision that treatment is necessary must be made, for a failed endoscopic procedure necessarily leads to its surgical counterpart. In this era of minimally invasive surgery, it is easy to allow lax surgical decision making; a critical appraisal of the place of interventional procedures in the treatment of chronic pancreatitis is therefore now appropriate.

The techniques open to the interventional endoscopist include sphincterotomy of the main or accessory pancreatic duct, insertion of a temporary nasopancreatic drain, placement of a stent at the ampulla or within the duct at the site of a stricture or fistula (so occluding the duct opening of the fistula), and removal of duct calculi. Such stones can be fragmented by laser or contact lithotripsy, or extracted by means of a basket. In conjunction with sphincterotomy the calculi can be disintegrated by extracorporeal shockwave lithotripsy (ESWL). The development of the miniscope, which can be passed along the pancreatic duct, gives potential for undertaking procedures directly on the duct. The vision of endoscopic surgery appears infinite, but the clinical reality is limited.

The role of drainage procedures of the dorsal pancreatic system in patients with pancreas divisum has been controversial since its clinical relevance was first postulated in the 1970s. Both surgical and endoscopic accessory duct sphincterotomy have yielded conflicting, but mostly disappointing, results[1]. Although the results of endoscopic stenting of the dorsal system have been more encouraging in patients with recurrent acute attacks of pancreatitis[2,3], the degree of pain relief in those with chronic ductal changes has been discouraging[2]. Stenting of the dorsal system would seem justified only when there is definite obstruction at the level of the accessory papilla, a situation rarely found in pancreas divisum. Opinions by leading gastroenterologists and surgeons remain deeply divided over the efficacy of endoscopic and surgical treatment in pancreas divisum; the debate is unresolved.

Recent reports on endoscopic stenting for single strictures or stones in the vicinity of the papilla of Vater describe more promising results[4,5]. In expert hands, technical success in over 90 per cent of procedures can be achieved with few serious complications[4]. The use of ESWL as an adjunct to endoscopic drainage seems to improve the result in those with calcific pancreatitis with stones in the main pancreatic duct, and it may broaden the indications in patients with more extensive disease[4]. Complete clearance of pancreatic duct stones can be achieved in 40–70 per cent of cases[6]. Pain relief following successful decompression of an obstructed ductal system is usually dramatic and current data[6] suggest that about half of these patients are free of pain for at least 2 years. Moreover, the extraction of newly formed stones in patients who develop a relapse often affords them further respite. Recurrent stricture formation, however, remains a problem requiring prolonged or indefinite stenting. Stents must be changed every 4–6 months to avoid clogging and septic complications[4]. There is also concern that prolonged stenting may enhance the pathological process of chronic pancreatitis[7]. Until long-term results are available, endoscopic stenting should be limited to localized obstructive disease near the papilla, preferably as a temporary measure or, as has been suggested by Cremer *et al.*[4], to serve as a therapeutic test in selecting patients for a surgical drainage procedure.

Cystic collections associated with chronic pancreatitis seldom resolve spontaneously and are often a major cause of pain[8]. Many of these cysts are intrapancreatic and communicate with the main pancreatic ductal system[9]. Percutaneous aspiration is, therefore, seldom successful and external catheter drainage may be complicated by a persistent external fistula. Several studies have reported a high success rate for

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endoscopic drainage of cysts contiguous with the stomach or duodenum, with few complications[8,9]. Cysts may be drained with a temporary nasocystic catheter, stented via the main or accessory papilla[10], or drained directly into the stomach or duodenum[8,9]. Only cysts bulging into the bowel lumen can safely be drained by direct incision with a diathermy needle, and so many cysts in chronic pancreatitis are not amenable to endoscopic drainage. However, the use of endoscopic ultrasonography may increase the number of cysts suitable for such treatment. Long-term follow-up is necessary to determine how many patients will eventually require surgical drainage operations for reaccumulation of cysts, or for associated main pancreatic duct or bile duct abnormalities. Nevertheless, the short- to medium-term results are encouraging enough to support endoscopic drainage as first line-treatment in selected patients.

It has been claimed that pancreatic fistula may no longer be a surgical disease[11]. Many fistulas are due to stenosis of the ampulla or stricture of the pancreatic duct in the neck of the gland. A sphincterotomy or stent insertion across the fistula can solve the problem and avoid surgical intervention with its attendant sacrifice of pancreatic tissue.

There are few reports on the efficacy of endoscopic stenting for biliary obstruction in chronic pancreatitis. The experience from the Brussels group[12] would caution against long-term stenting, as resolution of the stricture rarely occurs and frequent blockage may result in serious septic complications. Secondary biliary cirrhosis is a rare complication in chronic pancreatitis and a biliary drainage procedure is indicated only when there is persistent obstructive jaundice or recurrent cholangitis[13]. Surgical drainage remains the only definitive long-term treatment and endoscopic stenting should be reserved for medically unfit patients.

It is difficult at present to predict to what extent endoscopic interventional procedures will complement or replace conventional operations for chronic pancreatitis. Current data are limited to reports from a few expert referral centres and it is not clear what proportion of patients who require drainage procedures is amenable to endoscopic treatment. Endoscopic drainage of pseudocysts holds the best promise, but it seems that long-term stenting of the pancreatic and bile ducts is both impractical and inappropriate. The theoretically attractive concept that temporary stenting may assist in patient selection for surgical drainage remains unsubstantiated, except in the management of some fistulas.

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Review

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Prosthetic vascular graft infection

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The aetiology, diagnosis and management of prosthetic vascular graft infection are reviewed. The importance of contamination at the time of surgery as the crucial aetiological factor is highlighted. Staphylococcus epidermidis *is the causative organism in over 50 per cent of cases and the reasons for this are explored. Sound surgical technique, use of prophylactic antibiotics and the avoidance of a groin incision are emphasized as the most important factors in prevention of graft infection. Difficulties of diagnosis are highlighted and the diagnostic role of various imaging methods is assessed. Graft excision with extra-anatomic revascularization is presented as the conventional surgical solution, while the roles of less radical surgical solutions and non-operative management are discussed.*

Infection of a prosthetic vascular graft is a serious complication of vascular surgery that carries high morbidity and mortality rates. Although relatively uncommon, complicating only 1–6 per cent of all operations[1–5], the cumulative incidence of such infection may be underestimated because of the long delay that often occurs between the original operation and first manifestation of infection. The number of patients at risk will continue to rise with the increasing use of prosthetic materials and the widening indications for reconstructive surgery. At current levels of activity in the UK, about 300–400 patients a year may be expected to be affected by vascular graft infection.

Aortic graft infection carries a reported[1,3,6] mortality rate of around 50 per cent and, although the mortality rate of infrainguinal graft infection[3,6,7] is lower at around 10–25 per cent, the amputation rate consequent upon infection[7] approaches 80 per cent. In both situations hospital stay is invariably long, averaging 90 days in one Danish study[5], and may involve multiple operations. The costs of treating the small group of patients with graft infection are consequently high.

Pathogenesis

Prosthetic vascular grafts are foreign bodies and can harbour organisms within their interstices. Although infection of the prosthesis is unlikely to lead to disruption of the material itself, spread of infection to the native vessel produces inflammation with subsequent erosion and disruption of the artery–graft anastomosis. Haemorrhage or false aneurysm may result.

The majority of graft infections are thought to arise by contamination of the graft material at the time of its insertion[1,4,8] Haematogenous infection is less common than direct graft contamination[1], but it may explain the lag between operation and first manifestation of infection in some patients. In one series[1] this was over 1 year in >20 per cent of cases. Experimentally, haematogenous seeding is easy to reproduce[9,10].

Contamination may occur because of inadequate sterilization of the graft, a breakdown in theatre sterile technique, contact with the patient's skin or an intra-abdominal organ, deposition of airborne particles, or from bacteria residing within the native artery. Contamination by organisms from the skin of the groin is the most frequent cause of graft infection[1,4–6] In the series of Lorentzen *et al.*[5], no graft infections occurred in 425 patients undergoing reconstruction confined to the abdomen, whereas 62 graft infections developed in 1986 patients having a bypass involving a groin incision Staphylococci are common skin commensals and are the most frequent isolate from infected grafts[3,5]. The groin is a relatively dirty area, prone to intertrigo, and in obese patients the surgical wound lies deeply buried in folds of moist skin. The incision in the groin cuts across skin creases, tends to gape, and may disrupt lymphatic channels with subsequent development of a lymph collection. Consequently, both superficial and deep wound infections are frequent problems in this area[5,6].

The significance of bacteria residing within thrombus or atheroma in the native vessel is unclear[11–15]. The incidence of positive cultures at the time of surgery[12] may be as high as 43 per cent and the organism most commonly cultured from the aortic wall is *Staphylococcus epidermidis*, the commonest cause of graft infection. If intra-aortic bacteria were the main source of such infection, its incidence would be similar after aortoiliac and aortofemoral bypass, but this is not the case. Durham *et al.*[14], however, have estimated that, when peroperative arterial cultures are positive, the risk of developing a graft infection is around 10 per cent. Intraoperative cultures may also be made from the contents of 'bowel bags' used for the containment of small bowel during aortic surgery. In the series of Ernst *et al*[11], cultures of the fluid transudate were positive in five of 45 patients despite systemic administration of perioperative antibiotics.

Other potential sources of contamination of the graft are infected skin ulcers, gangrenous toes or an infected superficial wound[16,17]. In one series, Lorentzen *et al.*[5] found that 55 per cent of patients who developed a graft infection had a focus of infection identified before operation. Of particular interest is that in two of the six patients identified as having a urinary tract infection before operation, cultures from urine and graft tissue were identical. Four of 22 cultures of foot lesions also yielded the organism subsequently isolated from the graft. The mechanism of transfer of infection from distal limb sepsis is unclear, but could involve direct contamination (blood-borne or lymphatic spread) Evidence for lymphatic spread is conflicting; although groin dissection inevitably cuts across lymphatics (leading to lymphatic contamination of the operative field), cultures from the groin may not be positive[4,18]. However, organisms injected into the ischaemic hindlimb of dogs may be cultured subsequently from ipsilateral groin wounds[19]. Wound infection in close proximity to vascular graft material could lead to the development of graft infection by direct extension.

Operation on other organs at the time of aortic surgery may contaminate the graft and most authors advise against the simultaneous performance of a second surgical procedure[20,21]. The importance of airborne contamination may be underestimated[22] Thousands of bacteria-laden skin scales are shed every minute by the operating team, and conventional theatre

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clothing does not prevent all of these falling into the wound That staphylococci resident on the skin of hospital staff may be multiresistant to antibiotics is of special concern. Whatever the mechanisms of perioperative contamination, an important risk factor in the pathogenesis of graft infection is poor surgical technique[5,7,23]. Up to 50 per cent of graft infections are associated with a surgical complication such as graft thrombosis, wound haematoma or lymphocele.

Microbiology

Graft infection is usually bacterial, although a wide range of micro-organisms have been implicated, including fungi[24], mycoplasmas[25] and mycobacteria[2]. In early series of graft infections[1,3–5], *S. aureus* was the most frequently identified pathogen, being isolated in up to 50 per cent of cases. This pattern of infection appears to be changing: *S. epidermidis*, Gram-negative organisms and mixed infections are increasingly being identified as the cause of graft infection[2,6,26–29]. This change is similar to that observed after joint replacement and cardiac surgery. It may relate to the widespread use of prophylactic antibiotics against *S. aureus* and the increasing prevalence of Gram-negative organisms in the hospital environment. The rise may also relate to improved culture techniques or simply to an increase in the reporting of positive cultures because *S. epidermidis* is now regarded as a pathogen rather than a commensal.

It is known that *S. epidermidis* produces a slime that increases its adherence to biomaterials, encases the organism, and may thereby protect it from antibiotics[30]. Bandyk *et al.*[26] found 15 of 30 graft infections were caused by *S. epidermidis*. This organism is of low pathogenicity, which may explain the late manifestation of the majority of these infections; the mean interval between arterial surgery and clinical manifestation of infection was 41 months. These authors and others[31,32] stressed the importance of fastidious microbiological techniques for the successful isolation and culture of the causative organism. It is essential to take cultures from the graft material itself and for both broth and agar media to be employed. Sonication of the graft material to release micro-organisms increases the proportion of positive cultures[32]. In only two of the 15 cases in which graft material cultures proved positive were those of perigraft fluid or tissue positive[26].

Two further points deserve mention. First, in all published series of graft infections there is a high incidence of negative cultures despite convincing clinical evidence of infection. This may be due to inadequate and inappropriate samples being sent for culture, technical deficiencies in the laboratory, or because the majority of patients are already being treated with broad-spectrum antibiotics. Specimens for microbiological culture must be handled with care and alacrity if meaningful results are to be obtained. Second, superficial wound cultures may be misleading in the context of prosthetic vascular graft infection. In Goldstone's series[2] there was only a 70 per cent correlation between superficial wound and graft culture results. Patients with graft infection will usually have been in hospital for some time and will generally be receiving antibiotics; colonization of skin and wounds by hospital commensals becomes inevitable. Treatment of graft infection should not be based solely on the results of superficial cultures.

Prevention

Strategies for the prevention of infection are conveniently considered with respect to the periods before, during and after operation. Those who are debilitated, diabetic, uraemic, obese, on steroids or immunocompromised are at increased risk of infection. In these high-risk patients grafting is usually best avoided other than to save life or limb. In all patients vein is the preferred conduit because of the reduced risk of infection and the less serious consequences of any infection that may develop[23,33].

Antibiotic prophylaxis has been shown in randomized trials to reduce the incidence of wound and graft infection and its use is obligatory[6,34–37]. The choice of antibiotic and length of treatment are, however, controversial. The antibiotic used should be guided by local bacterial prevalence and sensitivities, remembering that most infections are caused by *S. epidermidis*, *S. aureus* and Gram-negative organisms[3,5,38]. Cephalosporins are widely used but their activity against *S. epidermidis* is variable. In the series of Bandyk *et al* [26], 19 per cent of patients were sensitive to penicillin G, 82 per cent to methicillin, 91 per cent to cephalothin, and 100 per cent to both vancomycin and gentamicin. Within 5 days of admission to hospital a patient's skin flora may be already multiresistant to antibiotics[30]. Vancomycin offers excellent cover against Gram-positive organisms and may be used along with gentamicin in any patient undergoing reoperative surgery. The ideal length of treatment is not known. A dose before operation is essential, but some authors suggest discontinuing therapy 24 h after surgery while others advocate treatment until all intravenous lines and catheters have been removed. A second dose during the operation is wise if blood loss is heavy or if surgery is prolonged. Antibiotic irrigation of wounds may reduce colonization but has little role as an addition to intravenous antibiotic therapy[35]. There are no published trials of the use of long-term antibiotic prophylaxis in an attempt to reduce the incidence of graft infection. Antibiotic-bonded grafts have yet to find their place in the clinical setting but show experimental promise[39–42]. Shue *et al.*[39] inoculated aortic grafts in dogs with *S. aureus*; when intravenous cloxacillin was used as prophylaxis the graft infection rate at 3 weeks was 80 per cent, but when the graft was impregnated with cloxacillin this dropped to 30 per cent. Antibiotic bonding to cement in revisional hip surgery has a well defined role, and it may be that bonding to vascular grafts will soon play an important part in the prophylaxis and treatment of graft infection

The groin wound is the most prone to infection following vascular surgery and, if reasonably possible, reconstructive surgery should avoid this area. Preoperative bathing in chlorhexidine or other antiseptics has its advocates[43,44], but the evidence for any benefit is conflicting[18]. Shaving the skin increases the rate of wound infection compared with the use of depilatory cream, but if shaving is preferred it should be performed as close to the time of surgery as possible[44]. The timing of angiography in relation to surgery has an important bearing on the incidence of wound infection. Landreneau and Raju demonstrated a reduction in wound infection[45] when surgery was performed within 24 h of angiography or, alternatively, when it could be delayed beyond 1 week. Preparation of the skin before incision should be thorough, using povidone–iodine or chlorhexidine, or both[44,46]. Adhesive skin drapes appear to increase the rate of wound infection[44].

The observation that up to 60 per cent of vascular graft infections are associated with an avoidable operative complication illustrates the importance of sound surgical technique[5,6,47]. Tissues should be handled gently, good haemostasis secured, and wound closure accurate. Haematoma, seroma and lymphocele all provide excellent culture media and are strongly associated with wound and graft infection[5] Routine vacuum drainage of groin wounds does not appear to prevent either lymphocele or wound infection[48]. Reoperation for early graft thrombosis or major haemorrhage significantly increases the risk of infection[6]. There are no trials comparing the use of a skin crease incision with vertical groin incision in an attempt to reduce local wound complications.

Vascular operations are usually performed in theatres of conventional design used principally for general surgery. This practice may be inappropriate if airborne contamination is as important in the development of vascular prosthetic infection as it is in joint replacement surgery. In orthopaedic operations, provision of ultraclean air has been shown to reduce the rate of deep infection[49] by 78 per cent and infection rates of < 1 per cent are routinely achieved. The use of double gloving, a no-touch technique and theatre clothing that is impermeable to bacteria would seem wise, and does not require the large capital investment of installing ultraclean air systems[22].

Intravenous lines and the urinary catheter represent potential sources of bacteraemia and it seems prudent to remove these at the first opportunity. Wounds should not be tampered with unnecessarily; in this regard, transparent dressings have much to recommend them, allowing inspection of the wound while maintaining a barrier to infection. In patients in whom cultures of the aortic wall prove positive, Durham *et al.*[14] recommended 10 days of intravenous antibiotics followed by at least 6 months of oral therapy, but most vascular surgeons do not routinely obtain cultures from the aortic wall and question this recommendation. Haematogenous seeding of infection to a vascular graft is a continuing risk for as long as the graft remains in place. Dental work, manipulation of the genitourinary or gastrointestinal tract and, particularly, angiographic examinations all carry a risk of infection It is sensible to cover all such procedures with antibiotics.

Clinical presentation

The clinical manifestations of prosthetic vascular graft infection are protean and may be surprisingly subtle, making prompt diagnosis difficult. Early diagnosis is important in improving the prognosis[50]. The majority of patients with a bypass involving the groin present with overt signs of wound sepsis such as abscess formation, development of a sinus track, cellulitis or graft exposure[6]. There is usually systemic upset, fever and leucocytosis. This pattern predominates in patients presenting within 1 month of surgery and diagnosis is not difficult. Less commonly, graft thrombosis, septic emboli, false aneurysm, or haemorrhage from the groin may indicate an underlying graft infection. In these situations the problem may not be suspected until reoperation when pus is identified surrounding the graft. These more insidious presentations appear to be associated with infection by the low-virulence organism *S. epidermidis*[2,26,51].

Infection of aortic prostheses is best classified into two groups, perigraft infection and graft–enteric fistula. In the series of Goldstone and Cunningham, 38 per cent of patients with aortic graft infection had a graft–enteric fistula[52]. Those with perigraft infection most commonly present with overt signs of wound sepsis, but may have an indolent illness with malaise, low-grade fever, raised erythrocyte sedimentation rate and mild leucocytosis. The most common manifestation of graft–enteric fistula is gastrointestinal bleeding, which occurs in about two-thirds of patients[52]. The other third present with signs of sepsis without evidence of bleeding. The bleeding from a graft–enteric fistula is usually acute and may be massive, although chronic gastrointestinal bleeding occurs in up to one-third of patients with a fistula. The nature of the bleeding is closely related to the type of fistula: patients with acute bleeding usually have an anastomotic fistula; those with a paraprosthetic fistula bleed chronically or not at all[2]. In some series of patients presenting with gastrointestinal bleeding who also had an aortic graft *in situ*, up to 75 per cent were found to have causes for bleeding other than graft–enteric fistula[52,53]. In general, however, it is wise to assume that the cause of bleeding in patients with an aortic graft is a graft–enteric fistula until proven otherwise.

Investigation

The initial investigation in patients with an infrainguinal graft should be ultrasonography. Perigraft fluid is suggestive of infection and ultrasonographically guided aspiration can confirm the diagnosis. The aortic segment is most effectively investigated using computed tomography[54,55]. Perigraft fluid, gas, soft tissue swelling or false aneurysm formation are all significant findings. Bowel wall thickening of >5 mm is diagnostic for graft–enteric fistula[55]. Guided aspiration of perigraft fluid allows microbiological culture to determine the significance of the radiological changes. This is of particular importance in patients presenting in the early period after operation, when the radiological changes of infection have to be differentiated from normal appearances after operation.

The role of indium-labelled leucocyte scanning is debatable[54,56,57]; it has a sensitivity of 80 per cent but false positives are common[54,56,58]. A development of the technique using indium-labelled immunoglobulin G has shown both improved sensitivity and specificity for infection[59]. Magnetic resonance imaging shows great promise and appears to be the best technique for defining the extent of graft infection[60–62]. Contrast sinography should be performed in all patients with an open wound or draining sinus.

Angiography provides little help in confirming the presence or extent of graft infection but allows visualization of the distal vasculature before planned reconstruction. It may also demonstrate graft thrombosis or a false aneurysm. Gastroscopy is mandatory in the patient presenting with gastrointestinal bleeding. More than half the patients will prove to have reasons for bleeding other than graft–enteric fistula[63]. The examination must include the third and fourth parts of the duodenum and first few centimetres of the jejunum to exclude a fistula. Occasionally the graft itself will be visualized, but more commonly an ulcer, bleeding point, or merely an inflamed patch of mucosa are the only clues to the presence of a fistula. Conventional barium contrast studies have no role in the investigation of a suspected aortoduodenal fistula[63].

Management

The management of prosthetic vascular graft infection presents a formidable problem. Arresting haemorrhage, preservation of the limb circulation and control of sepsis are the priorities. Orthodox management involves revascularization via extra-anatomic pathways and excision and debridement of infected tissue[2,52,63]. Recent reports have described the success of aggressive non-operative treatment and of less radical surgery[64–70]. Infrainguinal and aortic graft infection are best considered separately. In both situations supportive care should be intensive with high-dose antibiotic regimens and nutritional support where appropriate.

Infrainguinal graft infection

Once the diagnosis is established and the patency of the distal vessels determined, standard management involves excision of the graft and all infected tissue with vein patching of the arteriotomies. If the viability of the limb is in doubt, revascularization is undertaken through non-infected tissue using autogenous materials. If native vessels are patent, excision of the graft alone may be sufficient to control sepsis while maintaining limb viability. In patients without suitable distal vessels for a bypass, amputation is usually advised[7]. Complete excision of the infected graft at amputation aids healing of the stump. The mortality rate associated with infrainguinal graft infection[7] approaches 20 per cent. In the series of Kitka *et al.*[7] there was a particularly high mortality rate of 42 per cent in patients undergoing attempted limb salvage. The authors advised early amputation in patients with severe sepsis and ischaemia

Less extensive surgical solutions and non-resectional treatment have been successfully employed[64,67,69–73]. Calligaro *et al* [64] advise a graded approach to therapy. If the graft is patent it is preserved; if it is occluded subtotal excision is performed leaving a 4-mm cuff on the common femoral artery; if there is anastomotic bleeding the whole graft is excised. In all cases infected tissue is radically debrided, intravenous antibiotics are given, and the wounds left open and treated with povidone–iodine-soaked dressings. Using this protocol they have achieved a mortality rate of 11 per cent and an amputation rate of 13 per cent. Non-resectional approaches to the problem have included continuous antibiotic or antiseptic irrigation[67,71,72] and more recently the use of rotational muscle flaps to cover the infected groin wound[69,70]. Mixter *et al.*[69] achieved successful preservation of graft function in 20 of 21 patients using debridement, intravenous antibiotics and flap coverage Jorgensen *et al.*[73] obtained healing in 13 of 14 patients with groin infection with wound debridement and placement of gentamicin-impregnated collagen in the wound. The success of non-resectional therapy appears to depend on: (1) a patent graft; (2) localized infection, (3) no evidence of anastomotic disruption; and (4) surgical debridement of infected tissue

Aortic graft infection

Conventional management of aortic graft infection involves extra-anatomic bypass through a non-infected clean field and complete excision of the infected graft. Performing the bypass first has been shown to reduce both the mortality and amputation rates[74] Nevertheless, the lowest mortality rates reported[74,51] are 10–25 per cent while rates of up to 70 per cent are not uncommon[75]. The operative procedures may be combined or staged. In the latter case excision is performed 3–4 days after revascularization. In cases involving massive haemorrhage, however, control of bleeding must be the first priority. Revascularization normally involves an axillofemoral graft with anastomosis to the common femoral artery in cases of aortoiliac infection, and to branches of the superficial femoral or profunda femoris artery in cases of aortofemoral infection.

A considerable technical problem surrounds management of the aortic stump. Disruption may occur in up to 20 per cent of cases[51] and is almost always fatal. Thorough aortic debridement is essential and a two-layer closure using non-absorbable materials is advisable. Patching of the stump using omentum[76] or vascularized submucosal jejunal graft[77,78] may help reduce the risk of disruption. *In situ* aortic replacement has also proved successful using both autogenous[79,80] and prosthetic[81,82] materials. Ehrenfeld *et al.*[80] reported a mortality rate of only 13 per cent in 24 patients using autogenous materials. Walker *et al*[82] treated 23 patients with aortoenteric fistula by excision and *in situ* prosthetic replacement. They achieved a perioperative mortality rate of 22 per cent and 89 per cent of survivors were alive 5 years after surgery Jacobs *et al*[81] recommended *in situ* prosthetic replacement in patients with low-grade infection and negative perigraft and blood cultures. Extra-anatomic bypass is advised in patients with severe infection and positive cultures.

Partial excision may be appropriate in patients with localized infections confined to one limb of an aortobifemoral graft. Revascularization is then possible using femorofemoral crossover, a graft through the obturator canal[83] or an axillofemoral reconstruction. Non-resectional therapy, in which the infected graft is left *in situ*, has also proved successful[67,69–72] although its place in management is still to be defined. Localized groin infection may be treated by debridement and antibiotic irrigation[67,71,72], debridement and muscle flap coverage[69,70], or debridement and placement of gentamicin-impregnated sponge[73,84]. Treatment of panprosthetic infection is more problematic, although Quick *et al.*[65] reported success in three of four patients treated by continuous antibiotic irrigation

Conclusions

Prosthetic vascular graft infection presents a formidable diagnostic and therapeutic challenge, and carries a high mortality rate Prevention remains preferable to therapy. Future developments include defining the role of antibiotic-bonded grafts in preventing and treating infection, and determining the place of non-resectional therapy compared with *in situ* graft replacement or graft excision with extra-anatomic bypass

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Announcement

European Surgical Fellowships

Since 1990 the Council of *The British Journal of Surgery* has awarded European Fellowships, each holding a value of up to £3000. Four Fellowships were awarded in 1990 and three in 1991.

In 1992 the scheme was expanded to allow surgeons working in other European countries to visit the UK. Four fellowships were awarded in that year, to Mr D. C. Mitchell (London), Mr T. H. Brown (Manchester), Dr E. M. Targarona (Barcelona) and Dr B. Nardo (Bologna).

It is Council's intention to offer European Fellowships once again in 1993. Applicants should submit details of their proposed itinerary and its anticipated costs, together with a curriculum vitae and two letters of support from senior colleagues They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to the Company Secretary, Professor D. C Carter, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK, by 1 February 1993

D. C. Carter

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Metastasectomy

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The literature on metastasectomy abounds in anecdote and retrospective studies of non-randomized patients. In this paper, the published evidence concerning the efficacy of metastasectomy in the lung, liver, brain, gastrointestinal tract and omentum is reviewed to formulate practical recommendations for patient selection and treatment. At some sites metastasectomy can be recommended with little hesitation for more widespread application, but surgery for liver metastases should still be regarded with some reservation.

The idea that surgeons should endeavour to resect distant metastases of malignant neoplasms contains a degree of absurdity. The presence of metastases implies systemic dissemination of disease and the notion that surgery could be of any value in this circumstance, except perhaps in the palliation of some local symptom, might be considered as misplaced enthusiasm. However, metastasectomy has become one of the most common indications for major liver and pulmonary resection in the developed world, and reports of metastasectomy of almost every conceivable cell type from every major organ in the body can be found.

The role of surgery in controlling regional metastases within lymph nodes is well established for tumours such as squamous cell carcinoma of the head and neck, malignant melanoma, testicular teratoma and breast cancer. Lymph node dissection can prolong life by averting involvement of a vital structure such as the carotid artery or trachea, although for diseases such as carcinoma of the breast, in which locoregional disease by itself is rarely fatal, the exact influence of lymph node surgery on survival is still uncertain The purpose of this paper is to examine the role of metastasectomy for distant metastases (as opposed to regional node metastases) by reviewing the published evidence

Lung metastases

The first report of pulmonary metastasectomy appears to be that of Barney and Churchill in 1939, who described a patient presenting with a solitary lung tumour in whom a primary renal cell carcinoma was subsequently discovered on routine physical examination[1]. After nephrectomy and a period of observation the pulmonary metastasis was resected; the patient survived for 23 years and died from cardiovascular disease. Alexander and Haight reported a series of patients in 1947 who had undergone resection of solitary lung metastases from a variety of primary tumours[2], and since that time the indications for pulmonary metastasectomy have been extended to include other primary diagnoses and multiple metastases. The morbidity of the operation is low and the operative mortality rates in recent series[3–6] range from zero to 2 per cent. Several reports of long-term survival after pulmonary metastasectomy have appeared[7–9]

Osteogenic sarcoma

The treatment of osteogenic sarcoma was revolutionized in the 1970s by the introduction of chemotherapy using high-dose methotrexate and leucovorin rescue. This discovery, that preoperative chemotherapy could achieve considerable regression of the primary tumour, occurred at the same time as bioengineering developments that allowed *en bloc* resection of the residual tumour with endoprosthetic reconstruction of bone and joints. However, despite its impact in the adjuvant setting, chemotherapy has been unable to cure patients with established lung metastases; the duration of chemotherapy-induced remission is usually <18 months. Osteogenic sarcoma lung metastasis has thus become one of the most important indications for pulmonary metastasectomy in recent years Approximately two-thirds of patients with relapse in the lung after primary therapy have surgically resectable disease[10]; 5-year survival rates of between 21 and 39 per cent have been reported after metastasectomy, with or without further chemotherapy[4,11–14]. Goorin *et al.*[15] have reported long-term cure of lung metastases from osteogenic sarcoma using surgery alone, but the majority of patients in other series have probably also received cytotoxic chemotherapy, so that the contribution of surgery is difficult to assess. Winkler[16] has commented that thoracotomy is usually better tolerated by children than is a single course of cytotoxic chemotherapy. Surgical metastasectomy for osteogenic sarcoma and other chemosensitive childhood cancers, such as Wilms' tumour or Ewing's sarcoma, may be particularly indicated for relapses after chemotherapy, because the likelihood of a successful secondary response to chemotherapy is reduced. Not surprisingly, the results of surgical treatment of metachronous metastases arising after chemotherapy are inferior to those of multimodality treatment of synchronous metastases[16]. Survival after thoracotomy appears to correlate with the degree of chemotherapy-induced histological necrosis of the resected metastases[8,13,16]

Soft tissue sarcoma

Soft tissue sarcomas in adults also have a propensity to metastasize preferentially to the lung, but in this case the response rates to chemotherapy are inferior to those seen with osteogenic sarcoma or embryonal sarcomas Surgical metastasectomy is again an important treatment option for these patients, because 5-year survival rates of 10–50 per cent have been reported, although in general the results are inferior to those seen with osteogenic sarcoma[5,6,8,13,17]. Interpretation of the results of this procedure is difficult because the published data on pulmonary metastasectomy come from uncontrolled studies that are greatly influenced by case selection, patients who are most likely to be referred for surgical metastasectomy are those with slowly progressive solitary metastases without evidence of extrapulmonary disease. There are no controlled trials comparing surgery with no treatment, or with localized radiotherapy or chemotherapy, on which to judge the efficacy of surgical metastasectomy The limited data available[18] on the outcome of untreated pulmonary metastases, however, suggest that these are usually fatal within 2 years. The survival figures after pulmonary metastasectomy are certainly impressive, and there is some evidence that the survival curves may level out after about 5 years, indicating that a proportion of patients are being 'cured'[19]. Repeat operations for recurrent pulmonary metastases may also be valuable[3].

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Renal cell carcinoma

Only a small proportion of patients with lung metastases from renal cell carcinoma have solitary or surgically resectable metastases, probably of the order of 1–3 per cent. Survival rates 5 years after metastasectomy of up to 35 per cent can be achieved[20], with the best results seen in patients with solitary metastases; repeat operations may again have some benefit[21] Spontaneous regression of pulmonary metastases after nephrectomy is a well known but extremely rare phenomenon, only 67 cases were found in reviews of the world literature from 1928 by Freed *et al*[22] in 1977 and Fairlamb[23] in 1981. Spontaneous regression is not, of course, synonymous with cure, because some lesions may regress while others simultaneously progress, and regression may be only short lived. Indeed, only 12 of the 67 cases reported have documented 5-year follow-up. It has been pointed out that the likelihood of achieving spontaneous regression is much less than the operative mortality rate associated with nephrectomy, surgery to the primary tumour should probably be avoided in patients with multiple metastases because nephrectomy neither increases survival nor improves the quality of life in these cases[24,25]. For patients with a surgically resectable primary and a solitary metastasis, nephrectomy and metastasectomy is the treatment of choice

Other tumours

The role of metastasectomy in other tumours is more controversial Excellent survival figures of >80 per cent at 5 years have been obtained following resection of testicular teratoma metastases, even when active tumour was found within the teratoma deposits after chemotherapy[5] Van Dongen *et al.* consider that metastasectomy for testicular teratoma is primarily indicated for staging purposes, but it probably also confers some therapeutic benefit[19]. The situation appears to be comparable to para-aortic lymph node dissection after chemotherapy for teratoma, where surgery is useful both for staging and for increasing the likelihood of disease control, presumably because there is a subgroup of patients with residual disease confined to the resected tissues. The situation with malignant melanoma is less encouraging Resection of pulmonary metastases of melanoma appears to be associated with a universally poor outcome, with virtually no survivors at 2 years, and most authors are reluctant to recommend thoracotomy[8,26] Patients with lung metastases from carcinomas of the breast or colon may occasionally be suitable for metastasectomy, but this is a relatively uncommon indication[27] because the proportion of these with resectable metastases confined to the lung is only about 1 per cent Rates of survival at 5 years of 20–45 per cent for such patients can be obtained, however, perhaps reflecting the favourable natural history found in this highly selected group of patients with slowly growing lung metastases and no evidence of disease elsewhere[6,8,13,26]. Despite the difficulty in attributing prolonged survival to metastasectomy or to the natural history of the disease, patients with solitary lung metastases from colorectal carcinoma should certainly be considered for metastasectomy, because the morbidity rate is low and results from published series encouraging, provided there is no concurrent disease at other sites[28,29]

Prognostic factors

A number of authors have attempted to establish selection criteria for pulmonary metastasectomy by identifying factors associated with prolonged survival. Factors generally considered to predict a good outcome after metastasectomy are:

1 Histology other than melanoma[5,8,26].
2. Availability of effective systemic therapy[5,8,13,16]
3. Control of disease at the primary site[30].
4. Small number of metastases[11,13,17,30,31].
5. Complete surgical clearance[5,19,31]
6 Long tumour volume doubling time[19,32,33]
7. Long disease-free interval[13,26,31,34,35].

There is controversy among authors as to the relative significance of these. The importance of the histological type of tumour has already been considered Patients who tend to do best are those with tumours responsive to chemotherapy, such as testicular teratoma. Patients with melanoma fare badly, and those with carcinoma or sarcoma have intermediate results, osteogenic sarcoma being associated with better survival rates than adult soft tissue sarcomas.

The number and size of lung metastases resected are important prognostic factors in many series (independent of tumour histology), with the best survival rates seen in patients with fewer than four metastases[11,13,17,30,31] Others have found that surgical resectability rather than the number of metastases is important: if complete surgical clearance can be achieved, the number of lesions resected does not matter[5,19,31] Patients with unexpected hilar nodal disease or irresectable pleural disease, for example, have a poor prognosis, underlining the importance of performing careful computed tomography (CT) before operation. Control of the disease at the primary site and at other extrapulmonary locations is usually a prerequisite for metastasectomy; Pastorino *et al.*[30] have found that subsequent local recurrence at the primary site is associated with loss of control systemically, presumably because both are an expression of aggressive tumour biology

A long disease-free interval between diagnosis of the primary and appearance of the first lung metastasis correlates with good survival after thoracotomy in many series[13,26,31,34,35] and this criterion is frequently used in the selection of patients for metastasectomy. However, in other series across a variety of histological types, the disease-free interval was not found to be of prognostic importance. Patients with short disease-free intervals or with synchronous metastases have achieved survival after thoracotomy equivalent to that of those with long intervals[11,17,19,32]. Van Dongen *et al.*[19] have tried to explain this apparent anomaly by postulating that, because the successful establishment of distant metastases is time dependent, some rapidly growing tumours may present early with a solitary metastasis before multiple deposits have had an opportunity to develop and thus benefit from early metastasectomy. This hypothesis seems implausible, and a better explanation may lie in the relationship between disease-free interval and tumour volume doubling time. Tumours with a long disease-free interval tend to be those with long doubling times and thus relatively favourable prognoses. Tumours with a short disease-free interval, on the other hand, may be a mixture of lesions with short doubling times (poor prognosis) and long doubling times (good prognosis) because of the variability of the time to initial diagnosis and time to metastasis within the natural history of a tumour. Joseph *et al.*[18], Holmes *et al.*[33] and Mountain *et al.*[32] have argued convincingly that tumour volume doubling time, calculated from serial chest radiographs, rather than the primary–secondary interval should be used as a selection criterion so that metastasectomy is not denied patients with a long tumour volume doubling time despite a short disease-free interval. Unfortunately, the calculation of tumour volume doubling time is usually impractical because serial radiographs with assessable disease may be unavailable and tumour growth rates can be Gompertzian rather than constant. Whatever the biological explanation, the clinical observation that some patients with synchronous metastases or short disease-free intervals have a good outcome after metastasectomy is certainly important, and the opportunity of metastasectomy should not be denied on this criterion alone

In summary, pulmonary metastasectomy appears to be a well tolerated procedure that carries a low morbidity rate. It is undoubtedly associated with an occasional long-term cure, and probably affords enhanced survival for a further significant subgroup of patients with a variety of carcinomas and other malignant tumours The most important criterion for patient selection appears to be that of surgical resectability; if all the disease can be cleared, good survival can be obtained for patients with multiple as well as solitary metastases

Liver metastases

Liver resection for metastases of colorectal cancer has been pursued vigorously in many centres around the world over the past two decades. Interest in such surgery was kindled by studies of planned relaparotomy for colorectal cancer by Wangensteen in the 1940s and 1950s, in which a number of patients with solitary liver metastases appeared to benefit from liver resection[36]. Subsequent reports of carcinoembryonic antigen-initiated 'second-look' surgery appeared to confirm that some patients with solitary liver metastases achieved prolonged survival following liver resection[37,38]. Although the number of patients benefiting was small, the depressing overall survival rate of this condition fuelled continuing interest. There is now an extensive literature on hepatic metastasectomy that demonstrates that low operative mortality rates can be achieved with subsequent survival figures that appear promising when compared with the overall outlook for patients with liver metastases

Overall 5-year survival rates following hepatic resection range from 10 to 32 per cent in the major published series[39–57], the higher end of this range tending to contain patients undergoing resection of solitary rather than multiple metastases (*Table 1*). The risk of relapse within the liver or with extrahepatic disease after hepatic metastasectomy is high, many patients presumably having undetected residual disease at the time of surgery. Careful patient selection is thus crucial, requiring CT before operation and arteriography or intra-operative ultrasonography to exclude multifocal liver disease and extrahepatic disease. Nevertheless, the ability of current investigative techniques to detect liver metastases < 1 cm in diameter is poor Herein lies a paradox: more intensive patient selection leads to better results, but a smaller number of individual patients to whom the treatment can be offered

Prognostic factors

Most authors agree that the extent of liver involvement is an important predictor of outcome following surgical resection. Some have found that the total number of metastases is important, with poor survival seen after surgery for four or more[45,58,59]. Others have disagreed, finding that the number of metastases resected was irrelevant to subsequent survival and that the important factors appeared to be the percentage involvement of liver parenchyma and surgical resectability[43,56–60]. Bilobar *versus* unilobar involvement does not correlate with survival, provided all the disease is surgically resectable[45,56,59,61].

Table 1 *Survival following hepatic metastasectomy*

Reference	Year	No of patients	Operative mortality rate (%)	5-year survival rate (%)
Wanebo *et al*[39]	1978	27	7	28*
Foster[40]	1978	78	5	22
Blumgart *et al.*[41]	1979	9	11	(1 patient)
Logan *et al*[42]	1982	19	5	(4 patients)
Fortner *et al*[43]	1983	65	7	30*
Cady and McDermott[44]	1985	23	0	n.k.
Ekberg *et al.*[45]	1986	58	6	16
Adson[46]	1987	141	3	23
Gall[47]	1987	110	5	32†
Bradpiece *et al.*[48]	1987	24	8	n k
Nordlinger *et al*[49]	1987	80	5	25
Adloff *et al*[50]	1987	55	2	20
Di Giorgio *et al*[51]	1989	21	14	(4 patients)
Mentges *et al*[52]	1989	49	6	11
Scheele *et al*[53]	1990	226	6	24 (40)‡
Schlag *et al.*[54]	1990	122	4	10
Coppa[55]	1990	42	4	22
Doci *et al*[56]	1991	100	5	30
Vogt *et al*[57]	1991	36	0	20

n.k., Not known *Does not take operative mortality into account. †Excludes patients with incomplete resection margins. ‡Value in parentheses refers to the survival of those with complete resection and clear margins, the value of 24 per cent is deduced from the raw survival data presented for the patients undergoing metastasectomy overall

As with pulmonary metastasectomy, there has been debate about the significance of the disease-free interval as a prognostic factor Hughes *et al.*[61], in a multi-institutional study, found an improved actuarial 5-year survival rate for patients with a primary–secondary disease-free interval > 1 year (42 per cent) compared with those with an interval of ⩽ 1 year (24 per cent) ($P < 0{\cdot}01$) Many others have found no difference comparing surgery for synchronous *versus* metachronous metastases[43,45,54,56,60]. Bismuth *et al*[62] have suggested a practical compromise, recommending that a gap of 3–4 months be left between primary surgery and resection of synchronous colorectal metastases. Any subsequent surgery is preceded by intensive restaging investigations to exclude patients with rapidly progressing disease.

The stage of the original primary carcinoma also appears to correlate with survival after metastasectomy, as the 5-year survival rate associated with Dukes' B lesions is about 30 per cent, compared with 20 per cent for Dukes' C; similarly, a narrow margin of clearance at the time of surgery for the primary tumour is associated with a poorer outcome after metastasectomy[48,63]. Such adverse factors should not, however, be regarded as absolute contraindications to metastasectomy.

Objections to hepatic metastasectomy

Some caution is required when interpreting the apparent success of hepatic metastasectomy. Solitary or low-volume liver metastases can be associated with prolonged survival even if left untreated. For example, Wagner *et al*[64] studied a series of 252 patients with colorectal liver metastases and reported a 21 per cent 3-year survival rate in the 39 with untreated solitary metastases. Goslin *et al*[65] found a median survival of 2 years in untreated patients with fewer than four liver metastases and Daly *et al.*[66] corroborated this figure in a study of metastases involving < 20 per cent of liver volume. The occasional patient may survive beyond 5 years with untreated liver metastases[64,67]. These figures are not dissimilar to many published results of surgical resection for liver metastases[64].

Minimization of operative mortality is essential if liver resection for metastases is to be contemplated, because any late survival benefit could be negated by a perioperative mortality rate of 5–10 per cent. Some published series unfortunately fail to take operative mortality into account when calculating subsequent survival figures, or exclude patients in whom complete surgical clearance could not be obtained at laparotomy, thus tending to give an overoptimistic impression[39,43,47,53,68]. Operative mortality rates range from zero to 14 per cent in the literature, with 5 per cent being a typical figure in recent series. However, it must be emphasized that these results are from specialist units with a major interest in such surgery; if liver resection for metastases is recommended for more general application, a 'learning curve' associated with less impressive morbidity and mortality rates may occur.

Another objection to surgery for liver metastases is that non-surgical methods of treatment, which avoid the problem of operative mortality, may offer a reasonable alternative. Resection of hepatic metastases in patients requiring alleviation of liver symptoms is rarely beneficial, and a better approach is palliative care using analgesics Hepatic artery infusional chemotherapy in patients with low-volume liver disease appears to be associated with survival rates similar to those obtained in the published series of liver resection For example, Ekberg *et al.*[69] found a 15 per cent 5-year survival rate after intra-arterial infusion of 5-fluorouracil, and O'Dwyer and Minton[70] reported survivors beyond 5 years using regional chemotherapy with this drug. In a randomized trial of continuous hepatic artery infusion with or without surgical resection for resectable multiple liver metastases, Wagman *et* *al.*[71] were unable to demonstrate any improvement in survival gained by metastasectomy

The majority of patients with colorectal liver metastases have irresectable disease In the minority who have resectable metastases, particularly those with solitary metastases, there appears to be a subgroup that is genuinely benefited by hepatic resection, as the number of patients surviving beyond 5 years is greater than might be expected for those with untreated equivalent disease[62]. However, the enhanced survival of a few needs to be seen in the context of the lost survival of those suffering premature operative death at a time when they would otherwise have been asymptomatic and able to live for a median of a further 2 years. The case for liver resection has never been verified by a randomized trial and in view of the reservations outlined its place in the management of colorectal carcinoma should still be regarded as uncertain.

Brain metastases

The brain is another frequent site of metastasis for solid tumours, the most common primary being carcinoma of the lung. About 50 per cent of patients with brain metastases have a solitary intracranial tumour, and of these about 50 per cent will be resectable by virtue of surgical accessibility and the general condition of the patient. Surgical resection is an attractive concept, as metastasectomy in the brain is often relatively straightforward and associated with low operative mortality and morbidity rates Brain metastases tend to be well circumscribed tumours with a surrounding pseudocapsule of reactive gliosis; Cushing and colleagues were able to demonstrate in the 1920s that they could be readily enucleated from surrounding brain tissue[72]. This encapsulating behaviour is the usual pattern of the tumour–host interface of brain metastases even for tumours with very infiltrative patterns of growth in the tissue of origin[73].

In contrast to metastases in the lungs or liver, brain metastases frequently cause distressing and disabling symptoms even when very small, and a major impetus to undertaking surgical resection has been the desire to achieve rapid alleviation of such symptoms. A high percentage of patients undergoing resection of solitary metastases regardless of the primary histological type achieve immediate and prolonged improvement in neurological symptoms; in only about 12 per cent of cases is there a deterioration of performance status. Although many of the available data are retrospective and uncontrolled, and can be criticized because selection bias may have skewed the results, for comparable tumours the palliative benefit of brain metastasectomy appears to be considerably greater than that which can be achieved using radiotherapy or dexamethasone[74]. This finding has been verified by a randomized trial of surgery with postoperative irradiation *versus* irradiation alone for solitary brain metastases, in which a highly significant difference in Karnofsky performance status was found in favour of surgery. The median time that patients undergoing surgery remained functionally independent was 38 weeks, compared with 8 weeks in those receiving radiation alone[75].

In addition to palliation, the surgical treatment of brain metastases also appears to increase survival, probably by forestalling the development of fatal complications such as intracranial haemorrhage or raised intracranial pressure. In the randomized trial of Patchell *et al.*[75], the median survival of 40 weeks for patients undergoing surgery was significantly longer than the 15 weeks for those having radiation alone ($P < 0.01$). Some workers have found that patients presenting with metachronous tumours have a trend towards improved survival[76], although others have found no significant difference, admittedly in studies with small numbers[77,78]. Good survival results have been achieved in patients presenting with primary lung cancer and a single synchronous brain metastasis by surgical resection at both locations[78,79]. Long-term survivors beyond 5 years have been reported following excision of metastases from soft tissue sarcoma and from renal cell, breast and colonic carcinoma, sometimes involving more than one craniotomy over a period of time; useful palliation can be achieved even in malignant melanoma[77,79–85].

Patients with multiple metastases may also be cured by metastasectomy, the key factor being complete surgical resectability, as discussed previously for pulmonary and hepatic metastasectomy[86]. The majority of patients with multiple metastases, however, have irresectable disease and should be considered for brain irradiation. Patients with radiosensitive or chemosensitive tumours, such as small cell lung cancer, germ cell tumours or lymphoma, are similarly better treated by brain irradiation and/or systemic therapy. An exception to this rule may be patients with germ cell tumours of the testis who suffer relapse in the brain in the face of combination chemotherapy, because some chemotherapy agents do not penetrate the blood–brain barrier well, surgery may be the better option[86].

In summary, there is good evidence that metastasectomy is superior to irradiation for solitary brain metastases. About 25 per cent of patients with such metastases have surgically resectable lesions, and therefore operation should be recommended more often.

Gastrointestinal metastases

Malignant melanoma frequently disseminates to the gastrointestinal tract, and in autopsy studies gastrointestinal metastases can be found in about 60 per cent of patients dying from this disease. However, only 3–4 per cent of patients with melanoma develop symptomatic gastrointestinal metastases during life, usually presenting with a complication such as obstruction, intussusception, perforation, haemorrhage or, rarely, obstructive jaundice or cholecystitis. Diagnosis before operation may be difficult, but the majority will have evidence of metastatic melanoma at other sites. Klaase and Kroon[87] reported that 30 cases of gastrointestinal metastases developed in a series of 835 patients with melanoma; in only four was the bowel disease the first evidence of dissemination. The most frequent site of involvement is the small bowel, followed by the colon and stomach Deposits in the stomach classically appear as 'target' lesions at endoscopy, but gastrointestinal metastases may form ulcers, polypoid tumours or infiltrative stenoses[88].

The primary goal of surgical intervention is usually to deal with the relevant surgical emergency. In the majority, simple metastasectomy with resection of involved bowel results in resolution of symptoms; Khadra *et al.*[89] reported that 44 of 56 patients undergoing surgery for gastrointestinal metastases achieved complete relief of symptoms. The median survival after surgery for gastrointestinal metastases[87,89,90] appears to be about 1 year, but a number of survivors beyond 5 years have been reported; the actuarial 5-year survival rate in the series of Klaase and Kroon[87] was 19 per cent. Although the primary goal of this surgery may be palliation, a vigorous attempt to resect all macroscopic gastrointestinal disease is justified because of the possibility of achieving long-term survival for a proportion of patients

Omentectomy

Omentectomy for carcinoma of the ovary is added to this review for completeness. The rationale behind this procedure, which is usually performed as part of the primary surgical treatment of ovarian cancer before cytotoxic chemotherapy or at planned relaparotomy at the end of chemotherapy, is the concept of cytoreduction. Surgery alone is rarely adequate for this disease except for selected stage IA cancers, and cytotoxic chemotherapy (usually involving platinum-containing regimens) has become the principal treatment for the majority of patients. There are good theoretical reasons for believing that the lower the total tumour cell burden in a patient, the more effective such chemotherapy may be in obtaining complete remission[91,92]. Reducing the tumour cell burden by cytoreductive surgery before chemotherapy has thus become widely accepted practice and, as the omentum is known to harbour ovarian carcinoma metastases in up to 60 per cent of cases overall and in 20 per cent of clinically uninvolved omenta, omentectomy has been added to the standard operation of total abdominal hysterectomy with bilateral salpingo-oophorectomy, often in conjunction with multiple peritoneal, diaphragmatic and retroperitoneal lymph node biopsies[93–95]. The usual practice is to remove only the infracolic omentum but, in patients with macroscopic omental involvement, formal omentectomy including the gastrocolic ligament is probably preferable[96].

The concept of cytoreductive surgery to obtain minimal tumour cell burden is attractive, but it is uncertain whether there is evidence to suggest that it works in clinical practice. There is clearly a relationship between the likelihood of response to chemotherapy and the amount of tumour left behind at the time of first laparotomy. For stage I disease, patients undergoing suboptimal surgery appear to have worse survival rates than those undergoing total abdominal hysterectomy, bilateral salpingo-oöphorectomy and omentectomy. For example, Sevelda *et al*[97] reported a 5-year survival rate of 62 *versus* 84 per cent, respectively, in patients undergoing unilateral salpingo-oöphorectomy compared with those having hysterectomy, oöphorectomy and omentectomy However, the reason for this difference in survival rate is likely to be understaging of the suboptimal surgery group in this retrospective study and not any direct therapeutic benefit imparted by more radical surgery. For stage III or IV disease, optimal cytoreduction (defined as residual disease <2 cm in diameter) is again associated with better response rates to chemotherapy and improved survival rates in comparison with patients left with disease >2 cm in diameter[98–100]. This effect cannot be attributed to an anomaly of staging and may suggest that cytoreduction is important. An alternative explanation is that the different survival reflects different tumour biology rather than any benefit imparted by surgery, the tumours that prove impossible to clear surgically having an intrinsically worse biological behaviour than those amenable to surgery[101] This hypothesis is difficult to refute outside a randomized trial, but until such data become available the pragmatic approach is to assume that macroscopic tumour clearance is of therapeutic value and therefore the surgical goal

The concept of cytoreduction as an adjunct to chemotherapy has led to the next logical step in the treatment of ovarian cancer: second-look laparotomy. The rationale for performing a second operation at the completion of chemotherapy has been partly that of restaging, so that patients with residual disease can continue with further courses of chemotherapy, and partly therapeutic in giving the surgeon a second chance to achieve complete macroscopic tumour clearance[102–104]. Planned relaparotomy gives information of prognostic significance, because patients with secondary residual tumour have a worse outlook than those in complete remission The therapeutic value of second-look surgery is, however, difficult to determine[101,104], and there is controversy about whether it produces any improvement in long-term survival[103,105,106] Lawton *et al.*[106] reported 108 patients undergoing planned relaparotomy in whom total macroscopic tumour clearance was possible in 26, the median disease-free survival of the surgically cleared group was 17 months compared with 9 months in the remaining 82, but both groups did badly compared with patients achieving complete tumour clearance at first laparotomy. Redman *et al*[107] reported 24 patients with residual disease at first laparotomy who had early second-look surgery after three courses of chemotherapy and who underwent debulking to <2 cm residuum; the survival of this group was not significantly greater than that of historical controls with residual disease who did not undergo planned relaparotomy

Despite these reservations, omentectomy for overt or occult omental metastases should still be considered an essential part of the surgical treatment of ovarian cancer In early-stage disease it gives valuable staging information and in more advanced disease appears to have some therapeutic benefit as an adjunct to chemotherapy Planned relaparotomy may be of value as a staging procedure in selected patients, facilitating decisions about second-line chemotherapy. It may also be useful in palliation of symptoms due to bulk disease, but its ability to enhance survival by giving a second opportunity for cytoreduction is still unproven.

Conclusions

The literature on the subject of metastasectomy abounds in anecdote and retrospective studies of non-randomized patients, but a number of confident assertions can still be made. First, metastasectomy is undoubtedly of value in relieving symptoms caused by the local effects of a distant metastasis, particularly those in the brain or gastrointestinal tract, and should be considered the treatment of choice in these situations Second, there is a subgroup of patients for whom metastasectomy is also a means of prolonging life. For brain metastases this has been demonstrated in a randomized trial; for pulmonary, liver and gastrointestinal metastases it can be inferred from the observation of long-term cures in a significant minority of patients Third, metastasectomy can be recommended only when it can be achieved with low operative morbidity and mortality rates, as any long-term gain may otherwise be negated by short-term losses. It is for this reason that metastasectomy for lung and brain metastases can be recommended with little hesitation, although resection of liver metastases must still be regarded with some reservation.

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Digests

SURGERY TODAY
The Japanese Journal of Surgery

Br. J. Surg. 1992, Vol. 79,
December, 1275–1277

Having carried digests from The American Journal of Surgery *and* Der Chirurg *since March and April of this year, we this month extend our exchange to include* Surgery Today (The Japanese Journal of Surgery). *Professor Yoshio Mishima, Editor-in-Chief of that journal, has highlighted key papers from the January, March and May 1992 issues. A digest of the best of the* BJS *from July to September, prepared by our Editor, Professor John Farndon, will appear in the Japanese journal in December. Professor Mishima's address for correspondence is at the end of his summary.*

Surgical stress

Surgical insult, one of the more severe forms of stress, stimulates the most typical stress reaction. Abe *et al* [1] investigated these changes following surgery from an immunological viewpoint through cytokine and oxygen radical production in peripheral blood cells. Although the preoperative production of tumour necrosis factor (TNF) and interleukin 1 alpha (IL-1α) was raised, that of both lymphotoxin and interferon gamma (IFN-γ) were slightly suppressed. In the postoperative period the peak TNF, IL-1α and oxygen radical production was raised Lymphotoxin and IFN-γ production were suppressed in patients with an intraoperative blood loss >1000 ml. Thus, stress stimulates the macrophage–neutrophil system and suppresses the lymphotoxin and IFN-γ system (the inflammatory helper T cell system) in the early postoperative period.

Multiple organ failure (MOF) remains the most common cause of death after major operative procedures Infection and its systemic manifestations are the most important factors in the evolution of MOF. Inoue *et al.*[2] studied 36 patients undergoing major surgery to clarify the perioperative changes in polymorphonuclear leucocyte (PMNL) function and serum opsonin activity. In patients without postoperative infection, the PMNL phagocytic–bactericidal capacity and plasma elastase levels significantly increased, while the serum opsonin index fell. All parameters returned to preoperative levels within 1–2 weeks. Conversely, in patients with postoperative infection, the PMNL bactericidal capacity and plasma elastase levels remained high beyond 1–2 weeks, while the PMNL phagocytic capacity and serum opsonin index decreased substantially after 2 weeks. This result suggests that the most important predisposing factors to postoperative infection may be a depressed PMNL phagocytic capacity and a lower serum opsonin activity. The increased PMNL bactericidal capacity and high plasma elastase levels during postoperative infection may contribute to the susceptibility to MOF.

Paediatrics

The treatment of short bowel syndrome in children has been one of the most challenging paediatric problems of the past 20 years. Matsuo *et al.*[3] reviewed eight surviving patients from an original 15 children who underwent massive small bowel resection during the neonatal period All were able to be weaned from parenteral nutrition and six can tolerate normal meals. Two continue to receive enteral nutrition in the form of a low-residue diet at home. Near-normal somatic growth was achieved in the most recent five children, who received intensive nutritional treatment in the immediate postoperative period Three who did not receive nutritional management exhibited growth retardation; late metabolic complications such as renal calculi, cholelithiasis and pathological fractures were encountered in three children.

Oesophageal cancer

Anastomotic leakage is one of the most common complications of oesophagectomy and, since factor XIII is required for normal wound healing, Saito *et al.*[4] investigated the temporal changes in plasma factor XIII levels following oesophagectomy and hepatectomy. Plasma factor XIII activity decreased significantly in both the hepatectomy and control groups until day 7 after operation, reaching the lowest level on day 3 In contrast, the oesophagectomy group showed significant decreases in factor XIII levels throughout the postoperative study period, with a trough of mean activity of 56 per cent of the preoperative level on day 7. These results suggest that there is a marked and prolonged depression of plasma factor XIII activity following oesophagectomy.

An *en bloc* resection of oesophageal cancer includes resection of the thoracic duct. There is little knowledge of the pathophysiological changes after resection of this duct. Imamura *et al.*[5] examined 24 patients who underwent *en bloc* resection. Postoperative lymphangiography or computed tomography revealed abnormal collateral lymphatics around the kidneys or in the pelvic cavity, suggesting the development of lymphovenous fistulas.

Gastric cancer

Orita *et al.*[6] reported on 592 patients with early gastric cancer undergoing surgical resection. Thirteen patients died from recurrent disease. A careful analysis of these suggests that carcinomas that invade to the submucosa tend to recur more often than those confined to the mucosa. Well differentiated and papillary adenocarcinomas characterized by protruded or elevated lesions tend to recur earlier than poorly differentiated or signet-ring cell carcinomas characterized by depressed or excavated lesions. Both types recurred from haematogenous metastases, with the liver being the most common site. The macroscopic and histological features presently used to characterize early gastric cancer do not provide sufficient information to predict which patients are at most risk for recurrence.

Colorectal cancer

No operation for cancer of the colon or rectum should be carried out without thorough investigation of the whole of the large bowel. Maruyama *et al.*[7] analysed 149 patients with colorectal cancer. Thirteen (8·7 per cent) had extracolonic primary malignancy and ten (6·7 per cent) with multiple primary colorectal cancers were included. Curative resection was carried out in ten of the former 13 patients, while seven of the ten with multiple colorectal cancer underwent curative resection Nine patients in the former group were disease-free at 2 months to 14 years. Seven in the second group were disease-free at 1–22 years. The authors therefore recommend that, in any patient with colorectal cancer, the entire large bowel

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should be thoroughly examined for other primary tumours. Curative resection should be performed and follow-up should be for life

Adachi *et al*[8] investigated the antitumour activity and immunological effects of local administration of 5-fluorouracil (5-FU) by determining the tissue concentration of this drug, histological appearance of the primary tumour, and lymphocyte subsets of the regional lymph nodes in 23 patients with rectal cancer. Twelve patients were treated with 5-FU suppositories before operation, while 11 were given no preoperative treatment (the control group). The 5-FU concentrations in the primary tumours were higher than those in the regional lymph nodes and appeared to remain high for an extended period. No histological changes peculiar to the 5-FU group were observed in the primary tumours Analysis of the lymphocyte subsets in the pararectal nodes revealed that $\text{Leu2a}^{+}15^{-}$ cells, or cytotoxic T lymphocytes, were significantly decreased in number in the 5-FU group compared with the control group These results suggest that the local use of 5-FU may exert an antitumour effect and cause the suppression of antitumour immunity in the regional lymph nodes.

According to Nakamura *et al.*[9], of 30 patients undergoing hepatectomy for liver metastases from colorectal cancer, 17 had recurrence in the liver remnant during the following 12-year period. Six of these 17 patients underwent removal of isolated hepatic recurrences. Two of the six underwent a third hepatectomy, and three patients underwent partial lung resection on a total of five occasions. There were no operative deaths, although complications after a third hepatectomy contributed to a high morbidity rate of 40 per cent. The mean survival time of the six patients was 28·5 months from the second hepatectomy The prognosis of patients who underwent repeat hepatectomy was significantly better than that of those with irresectable recurrence after initial hepatectomy The overall 5-year survival rate of 29 patients excluding one in-hospital death was 45 per cent. These results suggest that aggressive removal of isolated and resectable recurrent disease has the potential to improve the prognosis of selected patients with metastatic cancer.

Hepatocellular carcinoma

Nagao *et al.*[10] analysed 23 patients with small hepatocellular carcinoma (a solitary lesion $\leqslant 2$ cm in diameter) undergoing hepatectomy. Hepatitis B surface antigen tests were positive in four patients; the preoperative serum alpha fetoprotein level was within the normal range in seven and slightly raised (20–200 ng/ml) in 14 Liver cirrhosis was present in 16 patients and chronic hepatitis in six. The diagnosis was suspected from periodic examinations, including ultrasonography and the measurement of alpha fetoprotein, in all except one patient. Minor hepatic resection was performed in 22 patients and lobectomy in one in whom the tumour was centrally located. Three patients died from hepatic failure in hospital following surgery, and the survival rates of the other 20 at 1, 3 and 5 years were 90, 79 and 61 per cent respectively Prognostic factors influencing long-term survival were investigated The only factor associated with a significant difference in survival was the severity of concomitant liver disease

Regarding hepatic functional reserve, Hamanoue *et al*[11] investigated the correlation between the arterial blood ketone body ratio (AKBR) and β-hydroxybutyric acid in the course of a 75-g glucose tolerance test. The correlation was revealed to be highly significant according to the equation:

$$\log[\text{AKBR}] = \text{A} + \text{B} \times \log[\beta\text{-hydroxybutyric acid}]$$

This was found in normal individuals and patients with liver, biliary tract or pancreatic disease. The postoperative course was unsatisfactory because of liver dysfunction in patients whose B value was more than $-0{\cdot}60$ in bisegmentectomy and above $-0{\cdot}45$ in unisegmentectomy or subsegmentectomy The coefficient B was suggested to reflect hepatic functional reserve.

Breast cancer

Tsuchiya *et al*[12] studied the relationship between oestrogen receptor (ER) status and DNA ploidy in 121 patients with breast cancer. Lymph node status was evaluated histologically and ER levels determined by the dextran-coated charcoal method, with a level of 3 fmol per mg protein being considered positive. Flow cytometric DNA content was analysed using paraffin-embedded tissue blocks. Overall, 63 per cent of specimens were ER positive. Sixty-one patients had diploid and 60 aneuploid tumours. A significant correlation between the ER positivity rate and diploid DNA content was found. Higher ER levels were seen in postmenopausal patients with diploid tumours than in those with aneuploid lesions. Nodal status was not correlated with ER positivity or ploidy The results indicate that ER levels are correlated with DNA ploidy and reflect the degree of functional differentiation.

Noguchi *et al.*[13] evaluated the relationship between regional lymph node metastases and DNA ploidy in 207 patients with invasive breast cancer A significantly higher incidence of aneuploidy was found in patients with a large T_3 or T_4 tumour, positive axillary lymph node status, more than four positive axillary lymph nodes or positive internal mammary lymph nodes. In a univariate study, overall survival was significantly correlated with tumour size, axillary lymph node status, axillary and internal mammary lymph node metastases, and DNA ploidy. In multivariate analysis, however, only axillary and internal mammary lymph node metastases emerged as important independent prognostic factors for survival. DNA ploidy did not appear to be an independent prognostic factor either in the entire series or in those with negative axillary nodes It was closely correlated with axillary or internal mammary lymph node metastases, and the axillary node-negative patients had an extremely favourable prognosis.

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Der Chirurg

Br. J. Surg. 1992, Vol. 79, December, 1277–1279

Professor Christian Herfarth and Dr Thomas Lehnert of Der Chirurg *have this month written résumés of the most interesting articles published in the German journal from July to September of this year. A reciprocal digest is to be published in their December issue.*

Oesophageal cancer

Squamous cell carcinoma of the oesophagus is rare in Germany. There is considerable debate on the optimal surgical treatment of patients with this condition and the role of perioperative radiotherapy, alone or in combination with chemotherapy, is not clear. *Der Chirurg* carries in its September issue seven articles by experts in this field from Japan, the USA, Belgium and Germany[1–6]. Most agree that the value of chemotherapy and/or radiotherapy has not been established and more prospective randomized trials are needed before clear guidelines can be produced.

The Oesophageal Cancer Study Group of the Chirurgische Arbeitsgemeinschaft Onkologie embarked on such a trial several years ago and reports its results[7] at a median follow-up of 34 months. This multicentre study set out to determine the value of preoperative chemotherapy. Inclusion criteria were histological demonstration of squamous cell carcinoma of the oesophagus, absence of distant metastases as determined by computed tomography and ultrasonography, absence of tumour infiltration of the trachea, patient age <68 years, no previous chemotherapy or radiotherapy, Karnofsky score >70 per cent, normal haematological parameters and normal renal and pulmonary function Patients consenting to participate in the trial were randomly allocated to operation alone or in combination with three courses of preoperative chemotherapy using 5-fluorouracil ($1\ \mathrm{g\ m^{-2}\ day^{-1}}$ for 5 days) and cisplatin ($20\ \mathrm{mg\ m^{-2}\ day^{-1}}$ for 5 days) Patients with tumours not responding to chemotherapy after the first treatment cycle were referred for immediate surgery. All other patients underwent operation 2–3 weeks after completion of chemotherapy. The surgical procedure included monobloc dissection of coeliac nodes and the posterior mediastinum including paratracheal and paraoesophageal nodes. Of 77 patients eligible for the study, only 46 consented to randomization and 31 were thus treated according to the patient's preference. Twenty-two patients were randomized to chemotherapy plus operation and 24 to undergo operation without preoperative chemotherapy. Endpoints of the study were tumour- or treatment-related death. One patient refused chemotherapy after randomization. Eight of 21 patients receiving preoperative chemotherapy had either a major response ($n = 7$) or complete remission ($n = 1$), while another eight had either no response or disease progression ($n = 4$ for each). Two of the 21 patients died during preoperative chemotherapy. The rate of resectability was 11 of 16 (69 per cent) for patients with chemotherapy plus surgery and 19 of 24 (79 per cent) for surgery alone. Curative (R_0) resection was achieved in seven of 16 (44 per cent) and ten of 24 (42 per cent) of patients respectively. Patients with combined therapy had a high incidence of severe postoperative pulmonary complications (48 per cent) compared with those treated by operation alone (37 per cent). The hospital mortality rate of randomized and non-randomized patients was seven of 34 (21 per cent) in the chemotherapy plus surgery group and four of 42 (10 per cent) in the surgery alone group. Survival was better for responders (median 13 months) than for non-responders (median 5 months) in the chemotherapy plus surgery arm and for patients with curative (R_0) compared with palliative ($R_{1/2}$) resections. No significant increase in survival was found when chemotherapy plus surgery was compared with surgery alone and this was true for randomized patients ($n = 46$) as well as for all patients ($n = 77$). This study group concluded that the preoperative chemotherapy regimen tested did not increase tumour resectability or survival. Because of severe side-effects from chemotherapy it was decided to abandon the trial. This multicentre trial demonstrates that prospective randomized studies are required for the evaluation of new treatment regimens

In another study, the diagnostic accuracy of endosonography for detection of lymph node metastasis and tumour infiltration was evaluated[8]. A total of 63 patients were examined using 7.5- and 12-MHz probes. Complete endosonographic examination of the oesophagus was achieved in 42 patients In 21 the instrument would not pass the tumour Endosonographic determination of the depth of tumour infiltration into the oesophageal wall and surrounding tissues was compared with histopathological findings in 38 patients. The sensitivity for determination of depth of tumour invasion was 74 per cent. Sixteen surgical specimens of the oesophagus were studied endosonographically in a water immersion bath. A total of 90 lymph nodes were detected. Histopathological examination of the same specimens revealed a total of 271 lymph nodes (metastatic involvement in 104) All except six lymph nodes identified by endosonographic examination in the water immersion bath were >5 mm in diameter. Histological findings revealed that 45 of 84 lymph nodes (54 per cent) >5 mm in diameter were malignant. The authors emphasize that to date no precise sonographic criteria can be described to distinguish benign from malignant nodes The *in vivo* study, however, revealed that endosonographic assessment of nodal status had a sensitivity of 84 per cent and a specificity of 44 per cent.

Pancreatic cancer

Metastatic disease in patients with solid tumours of the gastrointestinal tract generally limits the success of surgery The presence of microscopic disease subsequently giving rise to local or distant metastases is not recognized at the time that the primary tumour is removed. This is particularly true for carcinoma of the pancreas. A group from Ulm[9] studied the incidence of free malignant cells in the peritoneal fluid of 57 patients with pancreatic disease. Specimens for cytological analysis were taken from different sites within the peritoneal cavity at the start of the operation and again at the end of the procedure. The cytological diagnosis of the presence or absence of malignant cells was made by an observer unaware of the

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clinical diagnosis. Twenty-one patients operated on for chronic pancreatitis were correctly diagnosed as negative for malignant cells. Cytological evidence of malignant cells in peritoneal fluid was obtained in 12 of 36 patients with a histological diagnosis of pancreatic cancer. In patients with positive cytology, malignant cells were found in 74 per cent of samples taken at the beginning of the operation compared with 56 per cent positive samples taken at the end The presence of malignant cells correlated with tumour stage no free malignant cells were demonstrable in eight patients with stage I or II, but in 12 of 25 with stage III or IV disease. Specimens were not evaluable in three patients The presence of malignant cells in peritoneal fluid correlated with the development of peritoneal and distant metastasis, but survival at 15 months after operation was not significantly different for patients with or without free malignant cells in the abdominal cavity

Gastric cancer

Adenocarcinoma of the stomach has an annual incidence of approximately 30–35 per 100 000 in Germany The prognosis correlates with histological type, tumour infiltration, lymph node status and the presence or absence of distant metastasis In a retrospective study of 529 patients with gastric cancer treated between 1980 and 1988, an attempt was made to evaluate the prognostic value of additional parameters[10] to determine better which patients might be suitable for limited treatment Univariate analysis of survival confirmed the prognostic value of tumour infiltration depth and lymph node metastasis. Tumour size and grading had a lesser influence on prognosis In addition to these more conventional criteria, tumour cell dissociation (TCD) at the tumour margin and lymph and blood capillary invasion were studied. TCD was graded from 0 to 3 and was most severe in signet-ring cell carcinoma and undifferentiated carcinoma The 5-year survival rates of patients were 91·7, 61·4, 41·2 and 21·3 per cent with increasing TCD. The determination of TCD for intestinal-type adenocarcinoma yielded significant additional prognostic information In a multivariate logistic regression model, TCD provided significant additional prognostic data, whereas tumour grade did not

In another arm of the study, the prognostic value of blood and lymph capillary invasion was evaluated Using routine histological techniques, invasion of blood or lymph capillaries was demonstrable in 24 and 46 per cent of tumours respectively. The highest incidence of blood vessel invasion (41 per cent) and lymph vessel invasion (63 per cent) was found in undifferentiated carcinoma. Both parameters alone or in combination were found to be of prognostic significance ($P < 0·001$) in a univariate analysis of all gastric cancers and again provided significant prognostic information when evaluated in addition to tumour infiltration and lymph node status Tumour grade did not provide additional prognostic information These factors may provide valuable stratification criteria in future treatment studies

Surgery for trauma

Achilles tendon rupture is one of the more frequent tendon injuries caused by recreational sports activities Traditional treatment consists of suture of the ruptured tendon Authors from Switzerland[11] report results of a prospective randomized trial comparing traditional suture with a new fibrin glue technique in patients with unilateral, complete and closed rupture of the Achilles tendon Between January 1982 and December 1989, a total of 25 patients were randomized to suture fixation and 20 to fibrin glueing of the ruptured tendon Technically, the tendon fibres were combed out and realigned in several layers. The fibrin glue (Tissucol; Immuno, Vienna, Austria) was then injected into the tendon using a fine cannula All extremities were immobilized for a total of 6 weeks with gradual refixation from plantar flexion to a neutral position of the ankle joint Patients were followed for a mean of 49 months. Full activity was resumed after 7 months in the fibrin glue group compared with 9 months in the suture group; no patient had rest pain after glueing compared with four of 25 with sutured tendons. Dorsal and plantar flexion were better in the group treated by fibrin sealing, as was the cosmetic result. Three reruptures were observed in the suture group 8–12 weeks after operation, compared with only one rupture at 9 weeks following fibrin sealing. All four ruptures were caused by undue stress. The authors conclude that fibrin glueing of an acutely ruptured Achilles tendon is superior to traditional suture fixation They stress, however, that the technique is applicable only in the early period (within 24 h of rupture), because adhesions and resorptive changes preclude combing and proper reinsertion of the tendon stumps in injuries treated after this time.

Postoperative complications

In Germany more than 1 million people in the general population are older than 80 years. Many of these present with gastrointestinal emergencies With improved hospital facilities many elderly patients are considered candidates for elective surgical procedures. The postoperative course of these patients will be determined not only by the success of the surgical procedure, but by their general management. A group from Mainz[12] prospectively studied pulmonary complications in 2280 patients undergoing gastrointestinal surgery between March 1986 and December 1988. Elective procedures accounted for 63 per cent of all operations, with a 4·3 per cent incidence of pulmonary complications. In patients treated electively, the incidence of pulmonary complications was significantly higher in patients undergoing gastroduodenal procedures than in those undergoing colonic surgery ($P < 0·01$). In patients receiving elective treatment the incidence of pulmonary complications was related to the amount of blood transfused, length of the surgical procedure and length of preoperative hospital stay. In emergency cases, age, American Society of Anesthesiologists grade, associated disease, operative times, blood transfusion requirements and surgery of the upper gastrointestinal tract were all associated with a significantly higher incidence of pulmonary complications The authors conclude that, particularly in elderly patients, early correction of anaemia and a short preoperative hospital stay will help to reduce the incidence of pulmonary complications after surgery.

Biliary surgery

To drain or not to drain? This question has repeatedly been raised regarding the management of patients undergoing simple cholecystectomy Although various randomized studies have not demonstrated advantages of drainage, many surgeons still favour the insertion of a drain even after uncomplicated cholecystectomy Forster *et al.* set out to provide definitive information, applying strict criteria for operative and postoperative treatment[13]. Between March 1988 and June 1991, a total of 160 patients undergoing open cholecystectomy were randomized to drainage using an Easy Flow drain (Dow Chemical, Valbourne, France) placed at the foramen of Winslow or no drainage Patients with acute cholecystitis or choledocholithiasis were excluded from the study No significant differences were established in terms of postoperative wound infection, pyrexia or pneumonia The overall complication rate was 10 per cent in the group with drainage compared with 14 per cent in those without All complications were managed conservatively. Subhepatic fluid collections were studied by repeat ultrasonography. They were more frequent on the first day after operation in patients without drainage but not thereafter. No patient in either group developed biliary leak or subhepatic abscess. The authors suggest that drainage is not required after simple open cholecystectomy. How long will it take until we see a randomized study of drainage *versus* no drainage in patients undergoing laparoscopic cholecystectomy?

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The American Journal of Surgery®

In the last of our quarterly digests for 1992, Dr Hiram Polk has this month selected articles from the July to September issues of The American Journal of Surgery, *of which he is Editor. Correspondence should be addressed primarily to Dr Polk, although* The British Journal of Surgery *would be glad to receive a copy.*

Br. J. Surg. 1992, Vol. 79, December, 1279–1280

Peptic ulcer

The number of elective operations for duodenal ulcer is reduced but a number of problems continue regarding the proper and/or ideal treatment of the patient with chronic duodenal ulcer disease. The Karolinska group was one of the first to study effectively selective proximal vagotomy[1]. They provide a detailed follow-up of patients treated more than 10 years ago and conclude that the addition of pyloroplasty to selective vagotomy and to selective proximal vagotomy is associated with fewer poor results and a reduced reoperation rate. This was a meticulous study with a long follow-up period.

The definition of a giant ulcer has always had a personal component: 'The ones I treat are larger than the ones you treat!' Professor Chua and associates in Singapore examined a group of 62 patients with ulcers >3 cm in diameter and compared them with 476 other patients with benign gastric ulcer[2]. The very large ulcer is far more likely to bleed, less likely to perforate and much more likely to penetrate into contiguous organs. Furthermore, the likelihood of there being a cancer in the very large ulcers is greater than for the smaller ones. These issues are important for the surgeon contemplating operation on a very large ulcer and with respect to the intraoperative management of those findings.

Feeding tubes

Percutaneous endoscopic gastrostomy and jejunostomy have become an industry of sorts in the USA, with a large number of individuals in nursing homes having these procedures carried out to facilitate chronic care. There are many arguments on the pros and cons of the quality of life involved. It has been argued that distal placement of the feeding tube, i.e. through the jejunum as opposed to through the stomach, would minimize and/or eliminate aspiration This is a major complication of these treatment methods and is not altered by the sites selected for intubation. Aspiration is an underdiagnosed surgical illness and a paper by Kadakia *et al.* brings that into clear perspective[3].

Thoracic surgery

Incision of the diaphragm is an uncommon enough procedure to cause even the most experienced surgeon to take a deep breath and reconsider exactly how it should be done. The security of repair and the direction in which it is ideally placed are discussed in some detail by Arthur Sicular from his personal experience with a large practice at the Mount Sinai Medical Center in New York[4]. The illustrations are particularly

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informative and indicate a preferred incision directly through the septum transversum as being substantially superior to the circumferential incision, which was popular earlier

Vascular surgery

Vascular surgery continues to occupy the attention of many surgeons who look after an ageing population O'Riordain, Buckley and O'Donnell from Cork, Ireland, examined their experience with polytetrafluoroethylene (PTFE) and autogenous saphenous vein grafts in above-knee reconstruction for critical distal ischaemia[5]. They report more favourable results with autogenous saphenous vein but decide, as has been the case more often in the USA, that the reasonable salvage, patency, convenience and ease of use argue in favour of PTFE, preserving saphenous vein for later use either with peripheral ischaemia or with cardiac ischaemia.

The inflammatory abdominal aortic aneurysm is being recognized before operation as a result of increased use of computed tomography (CT). Leseche and colleagues from Clichy, France, studied 17 consecutive patients with this uncommon variant and concluded that the diagnosis is facilitated by CT. Aneurysm resection is the treatment of choice because the risk of rupture still exists, and the procedure seems to reverse the inflammatory process[6]. They recommended routine follow-up with CT to document resolution or progression of the fibrotic process after aneurysm resection

I believe that there is no more persistent concern in the entire field of vascular surgery than the sporadic and seemingly random recurrence of spinal cord dysfunction in patients undergoing thoracoabdominal aortic replacement The report of 150 consecutive patients treated at the Ochsner Clinic in New Orleans by Hollier and associates is a case in point[7] The protocol included minimization of ischaemia by complete intercostal reimplantation whenever possible, cerebrospinal fluid drainage, and maintenance of proximal hypertension during aortic cross-clamping They also used moderate hypothermia, high-dose barbiturates and tried to avoid hyperglycaemia It appears that the combination of methods is associated with a reduction in spinal cord dysfunction.

Orthopaedics

The use of artificial knee prostheses has grown widely in the USA, in part because of the growth of the ageing population. Induction of ischaemic injury during the course of the operation may occur and may be related to the need to use a pneumatic tourniquet. DeLaurentis and colleagues from Philadelphia assayed the relative indications for revascularization which would precede or succeed total-knee arthroplasty, these clinical indicators may be helpful to the surgeon who has been asked to see the patient in anticipation of knee prosthetic replacement[8].

Laparoscopy

Laparoscopy is obviously the booming business in American surgery and the second and third generation of reports provide interesting observations. Voyles and Tucker pursued the idea that 'stray current' occurs as a result of monopolar electrosurgery and provided an interesting analysis of the potential for unintended and unexpected complications of laparoscopy[9]. They conclude that the safety of electrosurgery can be enhanced by surgical education regarding the biophysics of radiofrequency electrical energy, technical choices in instruments using all-metal cannula systems, and engineering developments with a dynamically monitored system for insulation failure and capacitive coupling.

Transfusion

Babineau and associates at the New England Deaconess Hospital discussed a review of transfusion practices in their intensive care unit to determine how often the magical 10 g/dl level of haemoglobin needs to be altered[10]. There is a catechism, as it were, that this is the indication for transfusion in the chronically hospitalized patient in the intensive care unit. They point out that 58 per cent of all such transfusions failed to change the oxygen consumption and were of questionable benefit. This writer has some disagreement with that in theory and thinks particularly that the very elderly and/or patients with identified heart disease tolerate anaemia relatively poorly, and that there may be more to this than the authors concede.

Immunology

The medical literature has been filled with discussions of monoclonal antibodies for the treatment of a variety of illnesses, most popularly those that are directed toward products of infection, notably endotoxin. DiPiro and his group are among the leading doctors of pharmacy in the country and have worked in an imaginative way to classify these products and define their biochemical background and clinical potential[11]. There is a publicity and a legislative war regarding the approval of these products, and their cost (in the range of US $4000 (£2400) per dose per patient) has heightened the debate in an imaginable way Clearly there will be a place for these kinds of products and DiPiro has defined them in an organized and effective way that may well allow the clinician to pick and choose which will be most meaningful to their practice

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Mechanical properties of the aneurysmal aorta

The mechanical properties of the abdominal aorta were investigated non-invasively in 30 patients with aortic aneurysm and 11 with peripheral arterial disease. The distensibility of the aorta was measured using M-mode ultrasonography, permitting non-invasive assessment of the pressure–strain elastic modulus or aortic stiffness, E_p. *The median* E_p *value increased from 4·0 N/cm² in control subjects in their third decade of life* (n = *10*) *to 10·4 N/cm² in middle age* (n = *11*) *to 14·0 N/cm² in the elderly* (n = *13*). *In the presence of a normal diameter, peripheral arterial disease with aortic atherosclerosis had little effect on aortic stiffness, median* E_p *being 16·0 N/cm². Aneurysmal dilatation was associated with a significant increase in aortic stiffness, median* E_p *being 31·3 N/cm²* ($P < 0{\cdot}001$). *For aortas of normal diameter,* E_p *was at all ages dependent on mean arterial pressure. In patients with aortic aneurysms there was no clear relationship between* E_p *and mean arterial pressure or aortic diameter. Of the patients studied, 15 underwent aortic reconstruction; increasing aortic stiffness* (*log* E_p) *was associated with a decreased medial elastin content of the aortic biopsy* ($r = -0{\cdot}63$, $P < 0{\cdot}02$). *This study demonstrates the marked stiffness or inelasticity of dilated or aneurysmal vessels, part of which is attributable to the loss of elastin.*

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The decrease of vascular elasticity with age has been well documented using invasive methods and, more recently, magnetic resonance spectroscopy[1–5] The mechanical properties of the ageing aorta and other elastic arteries influence cardiac afterload, hypertension, pulsatile flow to the extremities and pharmacological response to nitroprusside[3,4,6]. Whether the loss of aortic elasticity is associated causally with atherosclerosis or calcification has not been established.

Atherosclerosis is more marked in the abdominal aorta, the thoracic vessel being relatively spared[7]. Aneurysms occur frequently in the abdominal aorta and their incidence appears to be increasing[8] Changing mechanical properties may be of importance in aneurysm formation, where degenerative change in the aortic wall permits dilatation and rupture The size of an aneurysm remains the best guide to the risk of rupture, although small aneurysms may rupture while many of larger diameter do not There is a need to discern which aneurysms are at greatest risk[9], assessment of the mechanical properties of the aorta might provide information on this. Abdominal aortic aneurysms (AAAs) are readily imaged by ultrasonography and the possibility of investigating the mechanical properties of the abdominal aorta using M-mode ultrasonography was investigated

The extent of change in arterial diameter depends on pulse pressure and the elastic properties of the artery, a relationship described as the pressure–strain elastic modulus (E_p)[10]. This is defined by the arterial blood pressures at peak systole (P_s) and end diastole (P_d) and the corresponding arterial diameters (D_s and D_d).

$$E_p = (P_s - P_d)[D_d/(D_s - D_d)]$$

E_p is a measure of the stiffness or lack of elasticity of an artery[10] It describes the magnitude of the change in blood pressure required to produce a given fractional stretch in the arterial wall.

The elastic properties of the arterial wall depend on the composition of the wall itself. The principal load-bearing component in the normal aorta is elastin, which is easily stretched[11,12]. If elastin is destroyed then the remaining collagen, which is several thousand times stiffer, renders the arterial wall much less elastic, this has been demonstrated experimentally[13]. The elastic properties of the arterial wall are non-linear the more an artery is stretched the more difficult it becomes to dilate it further[14], because as elastin fibres stretch so collagen fibres are recruited as load-bearing elements, producing a progessively stiffer artery[12,13]. Because the elastic properties of the arterial wall are non-linear, the wall tension at which the elasticity is measured becomes important. The relationship between intraluminal pressure (P_i), vessel radius (r_v), wall thickness (h) and wall tension (T) is described by Laplace's law A normal artery can be considered cylindrical and $T = P_i(r_v/h)$. Therefore the tension increases with increasing intraluminal pressure and arterial diameter or with decreasing wall thickness. The increasing radius and decreasing wall thickness observed in aneurysmal dilatation would increase the tension and hence modify the elastic properties of the arterial wall, i.e. E_p would increase irrespective of changes in wall composition. As an artery dilates and its shape changes from cylindrical to spherical the application of Laplace's law for a sphere becomes relevant, where $T = P_i\,(r_v/2h)$ The change of shape with localized arterial dilatation acts to reduce wall tension for a given radius. The net effect is that, even in the absence of alterations in aortic wall composition, wall tension and E_p would be predicted to increase as mean arterial blood pressure and arterial diameter rise, although these increases in wall tension and E_p are minimized by the change in shape from cylinder to sphere.

The relationship between elastin–collagen content and the mechanical properties of arteries has been extensively investigated in *in vitro* samples, which are less distensible than the same arteries *in vivo*[13,15–18] Assessment of the mechanical properties of the aorta in patients awaiting reconstruction for aneurysm or occlusive atherosclerosis provides the opportunity of comparing the distensibility of the aorta *in vivo* with the elastin–collagen content of an aortic biopsy This study estimates E_p, using M-mode ultrasonography, in young, middle-aged and elderly subjects, and in patients with AAA and peripheral arterial disease

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Patients and methods

The subjects studied included six young men and four young women of median age 25 (range 21–29) years, 11 middle-aged men of median age 55 (range 41–64) years and eight elderly men and five elderly women of median age 71·5 (range 65–91) years. None of the subjects was diabetic and all had diastolic blood pressure <100 mmHg, maximum external anterior–posterior aortic diameter <2·5 cm and ankle brachial systolic pressure index >0·9.

Patients with peripheral arterial disease included six men and five women of median age 69·5 (range 61–77) years. None was diabetic and the diagnosis of peripheral arterial disease was confirmed by a history of intermittent claudication and an ankle:brachial systolic pressure index <0·8. One patient underwent aortic reconstruction to bypass occlusive lesions of the aorta. Non-diabetic patients with AAA (aortic diameter 3–10 cm) included 25 men and five women of median age 74 (range 54–83) years. The majority underwent aortic reconstruction during the course of the study. All procedures were approved by the local ethical committee.

Arterial blood pressures were determined by sphygmomanometry at the brachial artery after 5 min rest (mean of three measurements) and after ultrasonography (mean of three measurements); pressure equivalence in right and left arms was checked. All blood pressures were measured by the same observer. The mean arterial pressure (P_a) was calculated as:

$$P_a = P_d + \tfrac{1}{3}(P_s - P_d)$$

The maximum external anterior–posterior aortic diameter was measured at peak systole, 4 cm distal to the superior mesenteric artery or at the widest diameter, using B-mode ultrasonography. The diameter change through the cardiac cycle was then recorded for a minimum of ten cardiac cycles using an Irex Meridian M-mode echocardiograph (Johnson and Johnson, Ramsey, New Jersey, USA) equipped with a 3·5-MHz probe. The maximum systolic and minimum end diastolic diameters were averaged from the M-mode trace using the digitizing tablet of a Kontron Cardio 200 computer (Kontron, Munich, Germany) for measurement.

At aortic reconstruction, biopsies were obtained from the level where E_p had been determined. The adherent thrombus, intima and adventitia were dissected from the biopsy specimen and the media stored at −20°C. Elastin and collagen contents were estimated as previously described[19,20].

Differences between E_p values for the various groups were analysed using the Mann–Whitney U test. The reproducibility of determination of E_p was assessed by calculation of the coefficient of repeatability, where 95 per cent of the differences between repeated measurements are less than 2 s.d. from the mean[21].

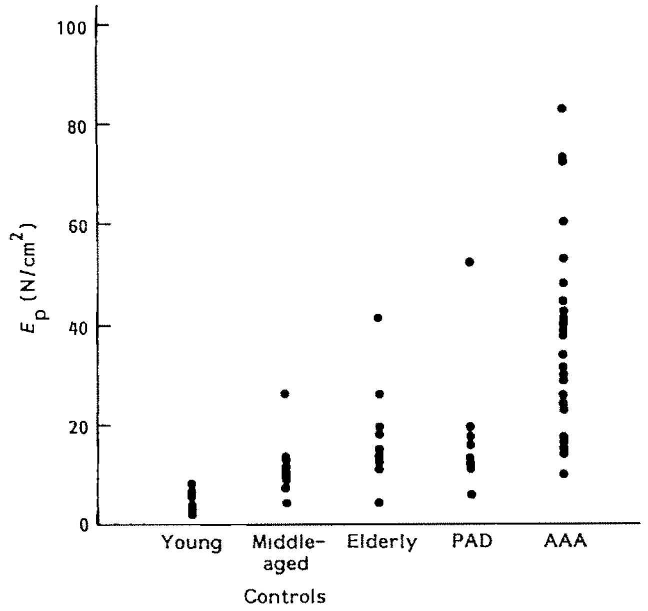

Figure 1 *Variation of the pressure–strain elastic modulus* (E_p) *of the abdominal aorta with age and peripheral arterial disease* (*PAD*) *or abdominal aortic aneurysm* (*AAA*)

Results

The aortic stiffness, E_p, for the normal subjects is shown in *Figure 1*. In the middle-aged controls this value was more than double that in the younger controls (median (range) 10·4 (4·5–26·3) *versus* 4·0 (2·1–8·1) N/cm^2, $P < 0{\cdot}02$). The aortic stiffness in the elderly controls (median 14·0 (range 4·3–41·4) N/cm^2) was over three times that of the younger controls ($P < 0{\cdot}01$). The coefficient of repeatability of E_p was 1·6 N/cm^2 for the younger controls but increased to 5 N/cm^2 for the elderly subjects. The calculation of E_p did not take into consideration the mean arterial pressure; for each group of controls there was a significant increase of E_p with mean arterial pressure (*Figure 2*).

E_p in patients with peripheral arterial disease and aortic atherosclerosis (median 16·0 (range 6·2–52·7) N/cm^2) was similar to that in the elderly age-matched controls (*Figure 1*). A linear relationship between E_p and mean arterial pressure was observed (*Figure 3*). The widest range of E_p was observed in patients with AAA, with a median of 31·3 (range 10·0–84·0) N/cm^2, E_p being significantly increased compared with either the elderly controls ($P < 0{\cdot}001$) or with the patients with peripheral arterial disease and aortic atherosclerosis ($P < 0{\cdot}01$). For the stiffest aneurysmal aortas, the coefficient of repeatability

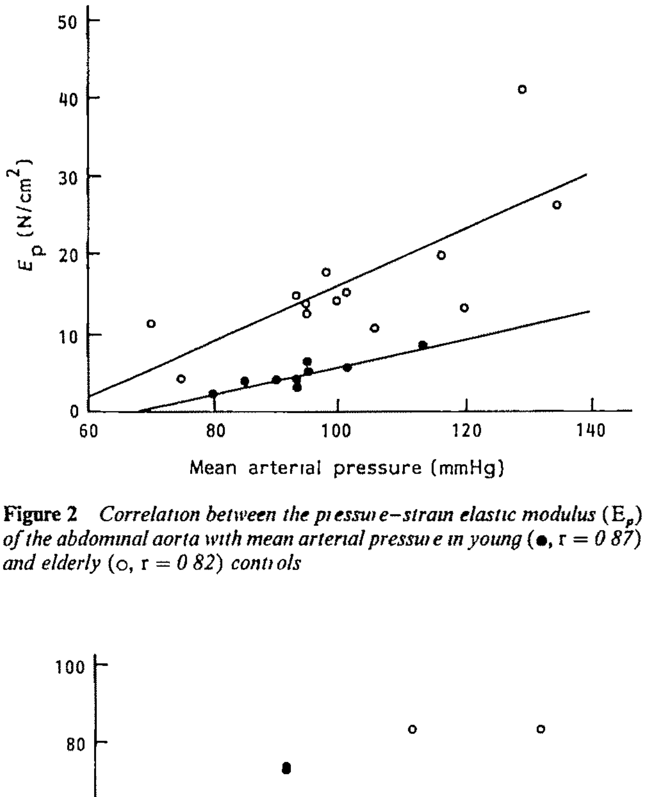

Figure 2 *Correlation between the pressure–strain elastic modulus* (E_p) *of the abdominal aorta with mean arterial pressure in young* (●, r = *0·87*) *and elderly* (○, r = *0·82*) *controls*

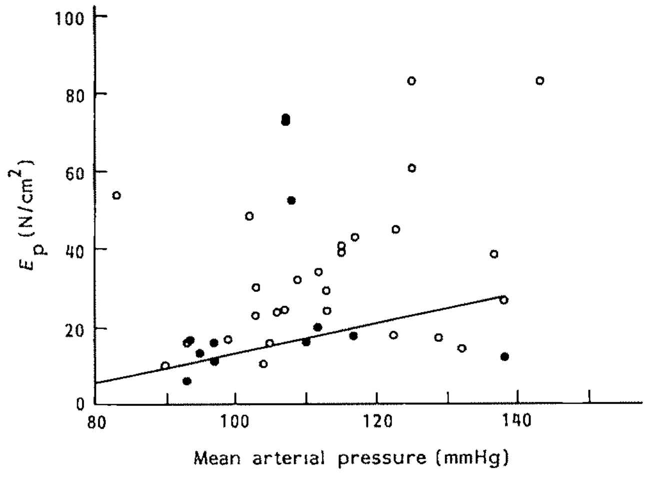

Figure 3 *Variation of the pressure–strain elastic modulus* (E_p) *of the abdominal aorta with mean arterial pressure for patients with peripheral arterial disease* (●) *and abdominal aortic aneurysm* (○) *The line for the patients with peripheral arterial disease has the same slope and intercept as that of the elderly controls* (Figure 2) *but the correlation coefficient* (r = *0·78*) *is lower*

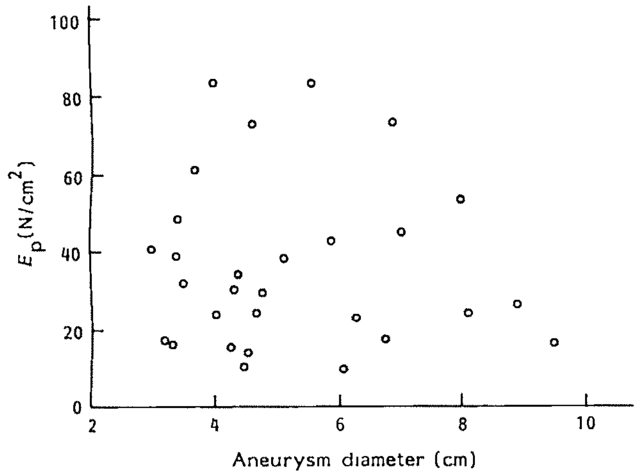

Figure 4 *Variation of the pressure–strain elastic modulus* (E_p) *with maximum infrarenal aortic diameter in patients with abdominal aortic aneurysm*

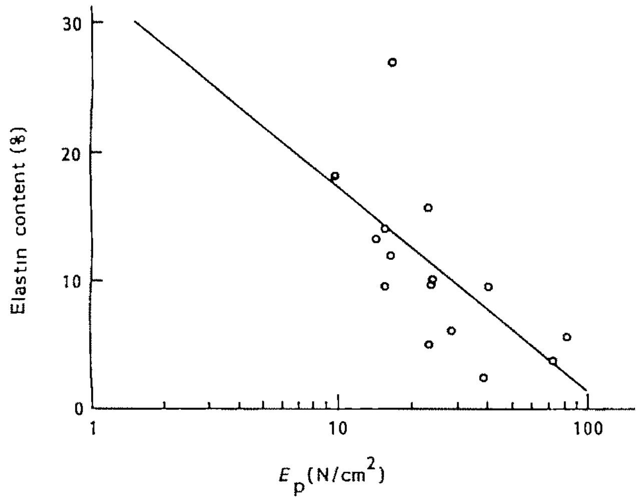

Figure 5 *Dependence of the pressure–strain elastic modulus* (E_p) *of the abdominal aorta on elastin content (percentage dry weight of the aortic media)* $r = -0.63$, $P < 0.02$

of E_p had increased to 15 N/cm^2 The mean arterial pressure of patients with aneurysm was similar to that of those with peripheral arterial disease but there was no clear relationship between E_p and aortic diameter in the former group (*Figure 4*).

Analysis of biopsies from 15 patients (14 with AAA and one with peripheral arterial disease and occlusive aortic atherosclerosis) indicated that increasing collagen concentration was associated with greater aortic stiffness and demonstrated that a reduced medial elastin content was significantly associated ($P < 0.02$) with increasing aortic stiffness (*Figure 5*).

Discussion

An increase in the stiffness of the abdominal aorta with age has been demonstrated *in vivo* either invasively or non-invasively using phase-lock echo-tracking devices linked to ultrasonographic equipment or magnetic resonance imaging[3,4]. Further investigations may include computed tomography, which provides information about the thickness of the aortic wall. Thin walls and aortic blebs have been associated with an increased risk of rupture[22]. An alternative approach would be to investigate the mechanical properties of the dilated aorta in individual patients. To be useful such a method would need to be widely available, non-invasive and cost effective; M-mode ultrasonography could satisfy all these criteria and might allow identification of those aneurysms at greatest risk of rupture.

This approach was validated by comparing E_p in three control groups of different ages The reliability of using brachial artery pressures determined by auscultation rather than micromanometry in the abdominal aorta to estimate E_p has been established previously[3]. The E_p values obtained in the three age groups were similar to those previously reported[1–5]. The coefficient of repeatability of these measurements was high, but in the context of such marked differences between groups was considered satisfactory

In the majority (70–80 per cent) of non-diabetic patients with occlusive atherosclerotic disease, symptoms are attributed to femoropopliteal disease; in 10–20 per cent symptoms are of aortoiliac origin[23]. Atherosclerosis is a generalized disease and all patients with intermittent claudication are known to have extensive aortic atherosclerosis[23]. In 10–20 per cent of patients the occlusive lesions in the aortoiliac segment are severe enough for aortic reconstruction to be considered. E_p, with its dependence on mean arterial pressure, was very similar in this group of patients to that in the elderly controls. The latter would have some aortic atherosclerosis, but the extent in patients with haemodynamically proven peripheral arterial disease is likely to be considerably greater. These results indicate that ageing processes (such as calcification, medial thinning, loss of elastin and accumulation of glycoproteins), rather than atherosclerosis, have important influences on the stiffening of the abdominal aorta.

The aneurysmal aorta is significantly stiffer, or less elastic, than undilated age-matched aortas with or without occlusive atherosclerosis. This marked alteration in mechanical properties may be related to the dramatic changes in structure. extensive disorganization and fibrous replacement of the media, and marked reduction in the dry-weight elastin content[24,25]. Enzymatic destruction of elastin in excised arteries is known to reduce elasticity markedly, and enzymatic destruction of elastin *in vivo* results in aneurysm formation[13,26] The elastic properties of the aneurysmal aorta are unlikely to be influenced by the deposition of laminated thrombus within the lumen, because the presence of intramural thrombus has little effect on the mechanical properties of aneurysmal aorta *in vitro*[24] Such *in vitro* studies have demonstrated the altered mechanical properties of the aneurysmal aorta. E_p through the aneurysmal portion was increased approximately twofold compared with the vessel proximal and distal to the dilatation[24] As an AAA enlarges, the significant remodelling of the arterial wall may accentuate posterior tethering of the aneurysm and result in non-uniform expansion of the aneurysmal wall during the cardiac cycle These effects may contribute to an apparent increase in E_p in some circumstances *in vivo*, but are irrelevant to the investigation of excised arteries[24]. The results of the present study, showing an increased E_p for the aneurysmal wall *in vivo*, are strongly supported by previous investigations of excised arteries[24]

There was a linear relationship between E_p and mean arterial pressure in all the controls and the patients with peripheral arterial disease, but the loss of a clear relationship between E_p and mean arterial pressure in patients with AAA requires explanation. Laplace's law would indicate that in the dilated aorta the increased wall tension would resist further distension by pressure, especially in the larger aneurysms The balance of forces at the dilated vessel wall will be influenced by the shape of the aneurysm, the thickness of the aneurysmal wall and the reorganization of the structural components of the vessel wall The complexity of these changes may account for the absence of a clear relationship between E_p and mean arterial pressure and aortic diameter in aneurysms those aneurysms with the greatest wall tension are likely to be those with the highest E_p and at greatest risk of rupture.

The pressure–strain elastic modulus for pure elastin *in vitro*[17] is thought to be 10 N/cm^2 and that for collagen 1000 N/cm^2 Extrapolation of the linear relationship observed between medial elastin content and log E_p would indicate a pressure–strain elastic modulus of 200 N/cm^2 in the absence of any elastin. This remains an order of magnitude less than the anticipated E_p for pure collagen The elastin content is thus a major determinant of E_p, but other cellular and structural components of the aorta contribute to its distensibility

Further understanding of the relationship between aortic diameter, wall tension and the structural changes underlying the altered mechanical properties of aneurysmal vessels could provide the information to identify those aneurysms at greatest risk of rupture.

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Long-term reduction of intimal hyperplasia by the selective alpha-1 adrenergic antagonist doxazosin

Studies have shown that α_1-adrenergic blockade reduces intimal hyperplasia in the rabbit aorta. In this study a selective α_1-adrenergic antagonist, doxazosin, has been used to examine whether this effect is persistent and dose dependent. Forty-eight New Zealand White rabbits underwent endothelial denudation of the abdominal aorta using a Fogarty balloon catheter. Test rabbits were given low-dose (2 mg) or high-dose (8 mg) doxazosin daily and all animals killed at either 1 or 12 weeks after the procedure. The aortas were harvested after fixation in situ *with 4 per cent glutaraldehyde and neointimal hyperplasia was measured, using an* x–y *digitizer, as the percentage reduction in luminal cross-sectional area. At 1 week after surgery, rabbits receiving the low dose had a median area reduction of 7·7 per cent and those receiving the high dose a reduction of 8·2 per cent; both had significantly less intimal hyperplasia than control rabbits, which had a median area reduction of 14·8 per cent* ($P < 0{\cdot}01$). *However, at 12 weeks, when compared with the 32·6 per cent reduction in the control group, only those rabbits receiving high-dose doxazosin had significantly less intimal hyperplasia, with a reduction of 5·5 per cent* ($P < 0{\cdot}001$). *It is concluded that selective α_1-adrenergic blockade significantly reduces neointimal hyperplasia, that this effect is dose dependent, and that it persists for at least 3 months.*

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During most vascular procedures a degree of endothelial damage is inevitable This is followed by smooth muscle cell proliferation, which can lead to varying degrees of restenosis and even occlusion. Pharmacological attempts to control this hyperplastic response have shown promising results in animal models, but a suitable agent has not yet been identified in humans. Recent animal studies have demonstrated that endothelial denudation and the subsequent intimal hyperplasia is accompanied by a selective increase in sensitivity to noradrenaline[1–4] This is associated with an increased affinity for noradrenaline in the α_1-adrenergic receptor of vascular smooth muscle cells and also an associated increase in turnover in the intracellular phosphatidylinositol cycle[5].

Many growth factors including platelet-derived growth factor (PDGF), fibroblast growth factor, epidermal growth factor, insulin-like growth factor, interleukin 1 and transforming growth factor are involved in the development of intimal hyperplasia[6]. Interestingly, some of these also act through the phosphatidylinositol cycle, byproducts of which lead to an increase in intracellular calcium concentration and stimulate protein kinase C to promote a series of phosphorylations, leading to cell mitosis[7]. This common pathway for α_1-antagonists and growth factors may explain previous studies showing a 40 per cent reduction in rabbit intimal hyperplasia with prazosin[8]. However, the duration of this effect is not established; nor is it known whether it is dose related

The aim of the present study was to test whether a more selective α_1-antagonist (doxazosin mesylate) might have an even greater effect than prazosin, to investigate the duration of this effect and assess whether it is dose dependent.

Materials and methods

Forty-eight female New Zealand White rabbits (weight 2·5–3 5 kg) underwent endothelial denudation of the abdominal aorta using a Fogarty balloon catheter Sixteen animals were treated with doxazosin (2 mg) and another 16 with doxazosin (8 mg) from the day of surgery until they were killed, a further 16 rabbits acted as controls The extent of intimal hyperplasia was compared at 1 and 12 weeks after endothelial denudation. Doxazosin was administered orally in a once-daily dosage, previous studies have shown that up to 40 mg per day can be given safely[9]

Endothelial denudation

The technique for endothelial denudation was a modification of that of Baumgartner and Studer[10] and has been previously described[2] Anaesthesia was induced with ketamine (25 mg kg^{-1}) and midazolam (2 mg kg^{-1}) and maintained with nitrous oxide (2 l min^{-1}) and oxygen (2 l min^{-1}) Through a groin incision the superficial femoral artery was mobilized and a transverse arteriotomy made A 4-Fr Fogarty catheter was introduced and advanced proximally for 16 cm, inflated with air and then withdrawn. This was repeated four times The superficial femoral artery was ligated and the skin sutured

Protocol

All rabbits were caged individually, given water *ad libitum* and fed normal chow Of the 48 animals, 16 were used as controls, with half being killed at 1 week and the other half at 12 weeks. The remaining 32 rabbits were given doxazosin at either the lower dose (2 mg, $n = 16$) or the higher dose (8 mg, $n = 16$). These two groups were then divided equally into those killed at 1 week and at 12 weeks There was thus a total of six groups.

1. Control group killed at 1 week ($n = 8$)
2. Control group killed at 12 weeks ($n = 8$)
3. 'Low-dose' group killed at 1 week ($n = 8$)
4. 'Low-dose' group killed at 12 weeks ($n = 8$)
5. 'High-dose' group killed at 1 week ($n = 8$)
6. 'High-dose' group killed at 12 weeks ($n = 8$)

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Tissue harvesting

Under general anaesthesia the internal jugular vein was cannulated and a 4 per cent glutaraldehyde solution infused at arterial pressure to fix the vasculature *in situ*. A total of 200 ml was infused over a period of 20 min and the aorta then exposed and clamped at the level of the renal arteries and at the aortic bifurcation. This segment of abdominal aorta was then excised and immediately placed in 3·7 per cent formaldehyde. This technique is a modification of that described by Clowes *et al.*[11].

Histology and morphometry

Tissue blocks of cross-sections of aorta were cut at a fixed point 2 cm distal to the renal arteries. The blocks were dehydrated with graded alcohol and embedded in paraffin wax. A total of 48 sections (one from each rabbit aorta) 4-μm thick were then cut in cross section, mounted on glass slides, and stained with haematoxylin and eosin.

Sections were then projected at a standard magnification using the Image Analysis System (Cambridge Electronic Design, Cambridge, UK). Computer-generated image analysis was used to measure the area of the neointima. All measurements were made by two observers in 'blind' fashion. The results are expressed as the percentage reduction of luminal cross-sectional area caused by intimal hyperplasia.

Statistical analysis

The reduction of luminal cross-sectional area caused by intimal hyperplasia for each rabbit was calculated and the median (range) percentage luminal reduction for each group derived. The Mann–Whitney *U* test was used for statistical evaluation of the differences in the development of intimal hyperplasia between the control and treated groups. Results are considered significant at $P < 0·05$.

Table 1 *Luminal reduction*

	Control	Doxazosin	
		Low dose	High dose
1 week	14·8 (6·6–40·0)	7·7 (2·7–10·1)*	8·2 (0·9–11·5)†
12 weeks	32·6 (18·1–44·8)	25·7 (5·5–50·3)‡	5·5 (2·7–16·2)†

Values are median (range) percentages. *$P < 0·01$; †$P < 0·001$; ‡P not significant (*versus* control group, Mann–Whitney *U* test)

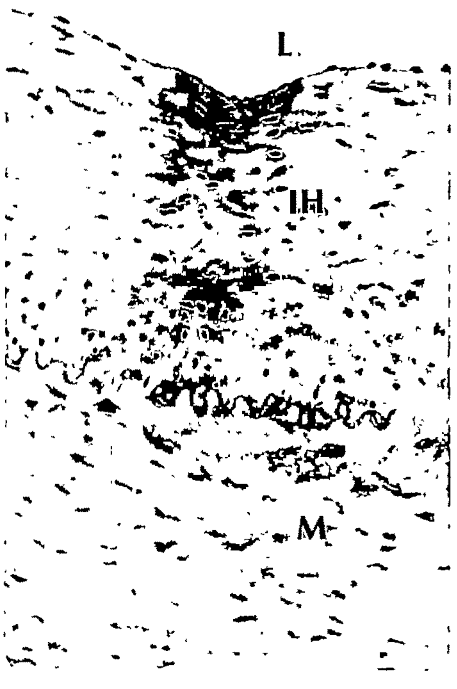

Figure 1 *Photomicrograph of a transverse section of control rabbit aorta 12 weeks after endothelial denudation showing many layers of smooth muscle cells in the neointima. L, lumen, IH, intimal hyperplasia, M, media. The arrow points to the internal elastic lamina (Haematoxylin and eosin stain, original magnification ×90)*

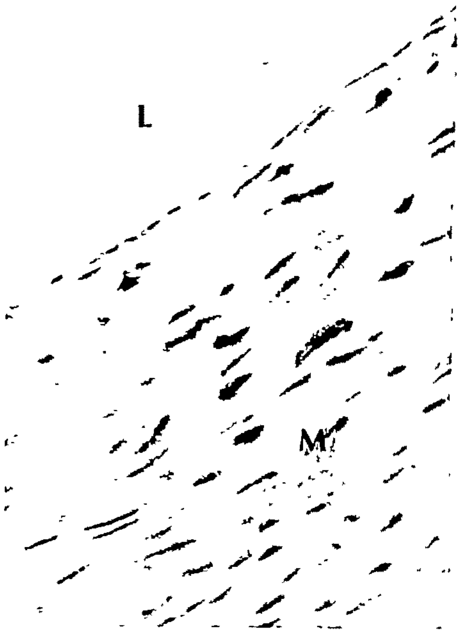

Figure 2 *Photomicrograph of a transverse section from a doxazosin-treated rabbit (high-dose group) 12 weeks after endothelial denudation showing minimal intimal hyperplasia. L, lumen, M, media. The arrow points to the internal elastic lamina. (Haematoxylin and eosin stain, original magnification ×150)*

Results

All rabbits survived the procedure and doxazosin was well tolerated. The results presented are therefore from all 48 rabbits. As in previous studies using this model, intimal hyperplasia was often asymmetrical. Rabbits killed at 1 week already showed early development of intimal hyperplasia with smooth muscle cell proliferation in the neointima, at 12 weeks the degree of hyperplasia had advanced significantly (*Table 1*). At this stage the neointima was lined by typical endothelial cells (*Figure 1*).

Both high- and low-dose doxazosin reduced intimal hyperplasia at 1 week but this did not persist in both groups at 12 weeks (*Table 1*). The median (range) reduction in luminal area in the low-dose group was 7·7 (2·7–10·1) per cent and in the control group 14·8 (6·6–40·0) per cent after 1 week ($P < 0·01$). However, the difference between these groups after 12 weeks was not statistically significant.

Intimal hyperplasia was also reduced with the higher dose of doxazosin. The median (range) reduction in luminal area was 8·2 (0·9–11·5) per cent at 1 week, statistically significant compared with 14·8 (6·6–40·0) per cent in the control group ($P < 0·001$). After 12 weeks, rabbits receiving the higher dose had developed significantly less intimal hyperplasia (*Figure 2*) than both control animals and those receiving the lower dose. The respective median (range) reductions were 5·5 (2·7–16·2), 32·6 (18·1–44·8) and 25·7 (5·5–50·3) per cent.

Discussion

Luminal narrowing from excessive intimal hyperplasia was first identified by Imparato *et al.* as a cause of late vein bypass graft failure[12]. Intimal hyperplasia has also been reported at endarterectomy sites[13], in prosthetic grafts[12,14], as recurrent stenosis after carotid endarterectomy[15] and in veins used in aortocoronary bypass grafting[16]. Less invasive procedures such as balloon dilatation angioplasty and mechanical atherectomy are also affected by intimal hyperplasia[17,18], the clinical significance of which may be even greater as it may also predispose to the development of atherosclerosis[19,20].

The rabbit is a suitable model for investigating intimal hyperplasia because endothelial denudation results in predictable smooth muscle cell proliferation[21]. Similar changes have recently been seen in human arteries after passage of an embolectomy balloon catheter (unpublished observations).

Several pharmacological agents have been used to modify the development of intimal hyperplasia. Aspirin and dipyridamole are frequently employed antiplatelet drugs. The results from many of the studies using such drugs have, however, been equivocal or contradictory and appear to be species dependent. A significant reduction in intimal hyperplasia has been shown in peripheral bypass in primates[22] and in canine aortocoronary bypass grafts[23]. However, antiplatelet therapy in rabbit aorta or canine peripheral bypasses has either no benefit[24] or actually increases the amount of hyperplasia[25]. The results from clinical trials are even more contradictory[26,27]. Calcium channel antagonists, anticoagulants and steroids have also been investigated in experimental and clinical studies, but without much success. The angiotensin-converting enzyme (ACE) inhibitors have caused significant reduction in hyperplasia after balloon denudation of rabbit aorta[28], a finding further supported by similar results in rabbit vein bypass grafts[29], but the reduction was less dramatic in the latter. Clinical studies with ACE inhibitors are awaited. Anticoagulants have stood the test of time and there is experimental evidence to suggest that heparin also reduces the development of hyperplasia[30], although controlled clinical studies are lacking

The results of the present study confirm the hypothesis that α_1-adrenergic blockade reduces the development of intimal hyperplasia and that this effect is dose dependent. The higher dose reduced the development of intimal hyperplasia significantly at 1 week and this persisted for up to 3 months. On the other hand, it is interesting to note that the lower dose was effective in reducing intimal hyperplasia in the short term but ineffective at 12 weeks. The reason for this is not obvious but may be that the initial mitogenic stimuli are derived from extrinsic sources (fibroblasts, platelets etc.) but after a few days smooth muscle cells are known to produce intrinsic growth factors capable of perpetuating this proliferation[31]. Therefore, as the intensity of the mitogenic stimulus increases, perhaps higher levels of the drug are required.

There is increasing evidence to suggest a role for α-adrenergic blockade when endothelial denudation is anticipated. First, there is increased sensitivity to noradrenaline in denuded aorta[1]; second, catecholamines can stimulate *in vitro* smooth muscle cell proliferation and this is mediated through α-adrenergic receptors[32–34], third, catecholamines can stimulate PDGF production in rat aorta[35]; and finally, α_1-adrenergic blockade can reduce the development of intimal hyperplasia by as much as 80 per cent. The developing association between adrenergic antagonists and smooth muscle cell mitogens is likely to be due to their common metabolic pathway, the phosphatidylinositol cycle.

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Surgical workshop

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Simplified method of subcuticular skin closure

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The use of subcuticular sutures is associated with a low rate of wound complications[1-3] Many surgeons retain such a suture by either taping the cut ends to the skin or knotting the suture over the skin for later trimming or removal. Others prefer to bury an absorbable suture completely in the subcutaneous tissues, with a knot used at either end of the wound.

For those concerned about wound complications, the first approach has the attraction that the suture can be withdrawn if a problem occurs. A buried knotted suture precludes easy removal even if the wound is opened.

A completely buried skin closure does, however, remove a potential portal of entry for infection and the wound will not require further attention, such as trimming of suture ends. A buried but knotless method of skin closure is presented.

Surgical technique

Undyed polydioxanone (PDS; Ethicon, Edinburgh, UK) is used with a straight cutting needle Closure is begun with the suture passed as a generous bite through the subcutaneous tissues Using the exiting suture as a retractor, the needle is then passed back through the exit point for a second bite of the subcutaneous tissues, before the needle is reversed to exit at the apex of the wound The wound is then closed in a normal subcuticular fashion At the opposite end of the incision the process is repeated (*Figures 1* and *2*)

Before the suture is cut, the wound is cleaned and dried, and suture tension adjusted Only then is the PDS cut flush with the skin, the ends being allowed to retract and the dressing applied Occasionally the lower end of a midline abdominal incision will gape a little, this is usually apparent before the suture is cut and a Steri-Strip (Ethicon) can be used to buttress the wound

Results

The use of knots with subcuticular skin closure is associated with ulceration through the skin in up to 17 per cent of cases[1]. The suture described requires no further attention. If infection occurs, the incision can be opened to allow the collection to drain and, if necessary, the suture material can then simply be removed in part or completely as no knot exists. In 247 wound closures, six patients have developed late gaping, all satisfactorily controlled with skin tapes Infections have been managed as described without undue complication.

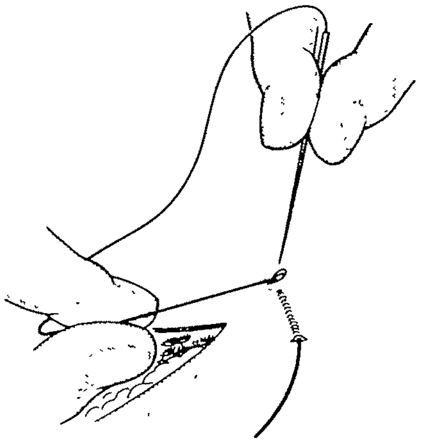

Figure 1 *The suture is used as a retractor to allow the needle to pass back through the exit point*

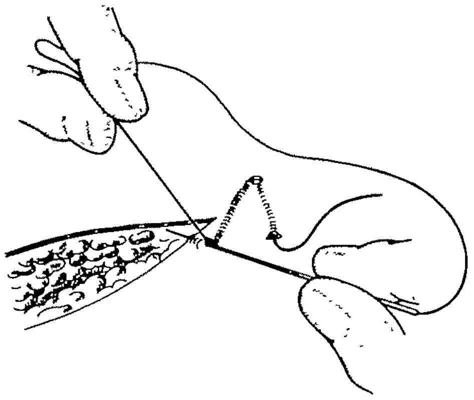

Figure 2 *The process is reversed, allowing the needle to exit at the apex of the wound*

The method is a little quicker to perform than other approaches and requires less subsequent attention

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Effect of free radical scavenging on skeletal muscle blood flow during postischaemic reperfusion

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After 6-h tourniquet ischaemia of one hindlimb in male Sprague–Dawley rats, gastrocnemius muscle blood flow was measured following 10, 120 and 240 min of reperfusion using radiolabelled microspheres. A perfusion index was calculated (experimental limb: contralateral limb) for each of these times. Comparison of perfusion indices in ten control animals (6 h ischaemia, 4 h reperfusion) with similar measurements in ten normal rats with no ischaemia and in ten ischaemic animals with the tourniquet in situ *demonstrated low median (interquartile range (i.q.r.)) reflow after 10 min (control 0·12 (0·02–0·43), ischaemia 0·04 (0·00–0·07), normal 1·05 (0·68–1·18); control* versus *ischaemia,* P *not significant; control* versus *normal,* $P < 0{\cdot}01$*). Relative reperfusion occurred at 120 min (control 0·48 (0·11–0·70), ischaemia 0·02 (0·01–0·07), normal 0·97 (0·79–1·13); control* versus *ischaemia,* $P < 0{\cdot}05$*; control* versus *normal,* $P < 0{\cdot}05$*) and reperfusion injury after 240 min of revascularization, with muscle blood flow being little different from that in the ischaemic group (control 0·05 (0·01–0·38), ischaemia 0·03 (0·00–0·07), normal 1·01 (0·73–1·16); control* versus *ischaemia,* P *not significant; control* versus *normal,* $P < 0{\cdot}01$*). Two groups of 12 rats were given either intravenous superoxide dismutase and catalase or dimethylthiourea 30 min before tourniquet release, continuing throughout the period of reperfusion. Superoxide dismutase and catalase reversed low reflow, producing a median (i.q.r.) perfusion index of 0·94 (0·54–1·12)* ($P < 0{\cdot}01$ versus *control,* P *not significant* versus *normal*)*, but had no effect on relative reperfusion (0·66 (0·42–1·01),* P *not significant* versus *control) or on reperfusion injury (0·27 (0·01–0·35),* P *not significant* versus *control). In contrast, dimethylthiourea had no effect on perfusion at either 10 min (0·10 (0·03–0·15),* P *not significant* versus *control) or 240 min (0·04 (0·00–0·11),* P *not significant* versus *control), but abolished the phase of relative reperfusion at 120 min (0·04 (0·02–0·21),* $P < 0{\cdot}01$ versus *control). These results indicate that, although superoxide radicals are harmful during postischaemic reperfusion, hydroxyl radicals may be beneficial.*

Failure of emergency vascular surgery to salvage an acutely ischaemic limb may be the result of skeletal muscle reperfusion injury. Such injury represents a progressive failure of the muscle microcirculation, leading to muscle infarction following a period of prolonged ischaemia and subsequent revascularization. Previous studies have demonstrated a triphasic pattern of skeletal muscle blood flow during revascularization following 6-h hindlimb ischaemia in a murine model of reperfusion injury[1]. Initial low reflow occurred immediately after revascularization and was followed by a phase of increased perfusion (relative reperfusion) at 2 h. However, muscle perfusion finally declined to negligible levels after 4 h, representing the onset of reperfusion injury.

Although the precise aetiology of reperfusion injury is obscure, it is likely that metabolic events occurring during the ischaemic period have an important role in its pathogenesis. During complete circulatory arrest, skeletal muscle adenosine 5′-triphosphate is degraded to hypoxanthine. A simultaneous rise in calcium ion concentration induces conversion of the enzyme xanthine dehydrogenase to xanthine oxidase. The action of the latter enzyme on hypoxanthine results in the generation of superoxide and hydroxyl free radicals[2].

Free radicals are highly reactive molecules, capable of disrupting muscle microcirculation in a number of ways. These include enhanced capillary permeability[3], damage to the endothelial cytoskeleton[4], neutrophil chemotaxis[5], and annihilation of the endothelium-derived relaxing factor (EDRF) nitric oxide[6]. Superoxide radicals are normally metabolized by intracellular superoxide dismutase and catalase[7] to produce water. These enzymes, when administered exogenously, act as superoxide radical scavengers. Similarly, dimethylthiourea is one of a number of compounds that have the ability to scavenge hydroxyl radicals[8].

The present model has been used to assess the relative roles of superoxide and hydroxyl free radicals in the alterations in muscle perfusion occurring during postischaemic revascularization. This has been achieved by the administration of free radical scavengers immediately before and during revascularization.

Materials and methods

Male Sprague–Dawley rats weighing 400–600 g were anaesthetized with 60 mg kg^{-1} intraperitoneal pentobarbitone. Tracheostomy was performed to aid tracheal toilet during the subsequent 10 h of anaesthesia, and cannulas were inserted into the left external jugular

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Table 1 *Gastrocnemius muscle perfusion index during reperfusion*

	No	Reperfusion time (min)		
		10	120	240
Normal	10	1·05 (0·68–1·18)	0·97 (0·79–1·13)	1·01 (0·73–1·16)
Ischaemia	10	0·04 (0·00–0·07)	0·02 (0·01–0·07)	0·03 (0·00–0·07)
Control	10	0·12 (0·02–0·43)†	0·48 (0·11–0·70)*‡	0·05 (0·01–0·38)†♯
Superoxide dismutase and catalase (superoxide radical scavengers)	12	0·94 (0·54–1·12)§	0·66 (0·42–1·01)	0·27 (0·01–0·35)
Dimethylthiourea (hydroxyl radical scavenger)	12	0·10 (0·03–0·15)	0·04 (0·02–0·21)§	0·04 (0·00–0·11)

Values are median (interquartile range). *$P < 0·05$ *versus* normal, †$P < 0·01$ *versus* normal, ‡$P < 0·05$ *versus* ischaemia, §$P < 0·01$ *versus* control, ♯$P < 0·05$ *versus* 120 min (Mann–Whitney *U* test)

vein (venous access) and the left ventricle (via the right carotid artery). A rubber-band tourniquet was applied to one hindlimb to produce total ischaemia, the contralateral limb acted as a control.

In three groups of experimental animals the tourniquet was left *in situ* for 6 h, the ischaemic period. At 30 min before revascularization, 12 rats were given an intravenous infusion of 35 000 units $kg^{-1} h^{-1}$ superoxide dismutase together with 400 000 units $kg^{-1} h^{-1}$ catalase, and 12 animals received 500 mg $kg^{-1} h^{-1}$ dimethylthiourea. Ten control animals received an infusion of normal saline. Ten normal animals to which no tourniquet was applied and ten with a tourniquet *in situ* were also studied.

After revascularization (tourniquet release), gastrocnemius muscle blood flow was measured at 10, 120 and 240 min (reperfusion time) by intraventricular injection of 15-μm radioactive microspheres (^{46}Sc, ^{85}St, ^{141}Ce, DuPont, Stevenage, UK). Animals were killed with an overdose of pentobarbitone at 240 min reperfusion, and the kidneys and gastrocnemius muscles harvested. Radioactivity in these tissues was measured using a Packard Auto-Gamma spectrometer (Canberra Packard, Pangbourne, UK). Adequate mixing of the microspheres with arterial blood in the left ventricle was confirmed by a ratio of radioactive emission of between 0·7 and 1·3 from the left and right kidneys. The ratio of radioactivity in the gastrocnemius muscles of the reperfused and contralateral normal limbs was calculated to give a perfusion index after appropriate corrections had been made for background activity and spillover from the three isotopes. Calculation of such an index assumes that blood flow to the contralateral normal limb is not influenced by systemic release of vasoactive mediators following reperfusion of the ischaemic limb. Although it is recognized that both the pulmonary and renal circulations may be susceptible to these remote effects, data from this laboratory have confirmed that muscle viability (assessed using nitroblue tetrazolium), capillary density and muscle oedema in the contralateral normal limb of experimental animals were no different from those measured in rats with no preceding ischaemia.

Statistical analysis was carried out using the Mann–Whitney *U* test with $P \leqslant 0·05$ taken as significant.

Results

The results are summarized in *Table 1*. The triphasic response in untreated animals has been described previously[1]. In normal animals, perfusion indices remained constant throughout the experiment, although in the ischaemic group blood flow was negligible at all times. Control rats subjected to 6 h of ischaemia followed by revascularization demonstrated low median (interquartile range (i.q.r.)) reflow (0·12 (0·02–0·43) at 10 min, $P < 0·01$ *versus* normal, P not significant *versus* ischaemia), relative reperfusion (0·48 (0·11–0·70) at 120 min, $P < 0·05$ *versus* ischaemia, $P < 0·05$ *versus* normal) and reperfusion injury (0·05 (0·01–0·38) at 240 min, $P < 0·01$ *versus* normal, P not significant *versus* ischaemia). The decline in muscle blood flow in control animals between 120 and 240 min was also significant ($P < 0·05$).

Superoxide radical scavenging

Administration of superoxide dismutase and catalase abolished low reflow (median 0·94 (i.q.r. 0·54–1·12) at 10 min, $P < 0·01$ *versus* control, P not significant *versus* normal). Despite this initial improvement in muscle perfusion, superoxide radical scavenging had no influence on the phases of relative reperfusion or reperfusion injury.

Hydroxyl radical scavenging

Perfusion indices in rats receiving the hydroxyl radical scavenger dimethylthiourea were similar to those of control animals after both 10 and 240 min of reperfusion. However, after 120 min of revascularization the median (i.q.r.) perfusion index of treated rats was significantly lower ($P < 0·01$) than that of control animals (0·04 (0·02–0·21)) and did not differ significantly from the index in animals with an ischaemic limb. Treatment with dimethylthiourea thus abolished the phase of relative reperfusion, implying that hydroxyl free radicals have a beneficial effect on skeletal muscle blood flow during postischaemic revascularization.

Discussion

This model demonstrates a triphasic pattern of muscle blood flow during revascularization that culminates in reperfusion injury. This sequence of events mirrors clinical changes that may occur following emergency vascular surgery and might be expected to compromise graft or limb survival[9]. Reperfusion injury represents a failure of the muscle microcirculation and thus alterations in surgical technique are unlikely to improve limb salvage rates. Furthermore, unpublished data from this laboratory have failed to confirm a role for fasciotomy in improving postischaemic muscle blood flow in this model, suggesting that tissue destruction is mediated by factors other than a simple rise in compartment pressure. A clearer understanding of the pathophysiological mechanisms responsible for the alterations that occur in blood flow may lead to effective pharmacological manipulation of these changes.

Low reflow

The pathogenesis of low reflow is uncertain[10], but it becomes more severe as the duration of ischaemia increases[11] and is always followed by a period of relative reperfusion[12,13]. Plugging of capillaries by neutrophils has been suggested as being responsible for low reflow[14], but it is difficult to explain its spontaneous recovery if this is the case. Furthermore, histological studies of muscle from experimental animals killed 10 min after tourniquet release do not show evidence of intravascular thrombosis or neutrophil plugging (unpublished data). This supports the findings of Makitie[15], although conflicting results have been reported[14,16].

It would seem more likely that the spontaneous recovery of low reflow is the result of a reversible vasoconstriction, and Feng *et al.*[10] have produced evidence that favours this. Further support for such a hypothesis is presented in the present study by the results of superoxide radical scavenging, which clearly implicate superoxide radicals in the pathogenesis of low reflow. Gryglewski *et al.*[6] have shown that superoxide radicals annihilate the EDRF nitric oxide, and this could be the mechanism by which low reflow is mediated. Consistent with this is the recent observation that the main site for free radical production is the capillary endothelial cell[17]. Although this hypothesis is attractive, it has also been suggested that superoxide radicals may themselves act as vasoconstrictors[18]. Such a role for superoxide radicals in the pathogenesis of low reflow may be simplistic in view of their possible ability to promote the release of an endothelial vasodilator[19], perhaps as the result of an interaction with EDRF, producing nitrogenous and hydroxyl radicals[20] This may explain the apparently beneficial role demonstrated for hydroxyl radicals. Although the pathogenesis of low reflow remains uncertain, superoxide radicals appear to have a central role.

Relative reperfusion

Gastrocnemius muscle blood flow at 120 min in rats receiving dimethylthiourea was significantly less than that in both control animals and those receiving superoxide scavengers ($P < 0.01$). Thus, dimethylthiourea abolished the phase of relative reperfusion. Such an action could be explained by the ability of hydroxyl radicals to promote prostanoid synthesis from cell membrane arachidonic acid of both neutrophils and endothelial cells[21,22], although the concomitant release of leukotrienes and thromboxane A_2 should antagonize the action of vasodilator eicosanoids.

Despite the findings of the present study, it must be admitted that the role of hydroxyl radicals in the deleterious effects of postischaemic reperfusion is confusing. In part, this may reflect the lack of a specific hydroxyl radical scavenger Although dimethylthiourea scavenges hydroxyl radicals, it also destroys hypochlorous acid and decomposes intracellular hydrogen peroxide, from which hydroxyl radicals are generated. Thus, although Carrea *et al.*[23] concluded that a reduction in the area of muscle infarction during coronary reperfusion was the result of scavenging hydroxyl radicals, McCutchan *et al.*[24] have suggested that the destruction of intracellular hydrogen peroxide may be of greater importance.

In support of the present findings, Zimmerman *et al.*[25] failed to reduce neutrophil infiltration of revascularized intestine (for which oxygen radicals are essential precursors) after administration of the hydroxyl radical scavenger dimethylsulphoxide. Although more specific scavengers may clarify the role of hydroxyl radicals in postischaemic tissue injury, it is possible that their action, either beneficial or harmful, may depend on other physiological influences.

Reperfusion injury

The pathogenesis of the final fall in muscle blood flow (reperfusion injury) is also unclear, but this decline is widely believed to be the result of mechanical occlusion of capillaries by neutrophils[14], endothelial swelling[26] or platelet aggregates[27]. Red cell sludging has also been observed in the capillaries of reperfused skeletal muscle[28], although this may simply reflect a reduction in plasma volume consequent on changes in vascular permeability. Alterations in the endothelial cytoskeleton, the expression of cell surface cytokines[29] and adhesion molecules[30], and the elaboration of endothelial vasoconstrictors[31] have been suggested as alternative mediators of reperfusion injury. Further studies to define the relative importance of these mechanisms are awaited.

In summary, the present experiments represent an animal model of acute lower-limb ischaemia demonstrating both low reflow and reperfusion injury following revascularization; such alterations could limit the success of surgery. Furthermore, it has been shown that superoxide radicals are mediators of low reflow, but that hydroxyl radical release during reperfusion may be beneficial.

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Case report

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Acute testicular torsion following orchidopexy for undescended testis

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Case reports

Patient 1

A 33-year-old man presented with a 6-h history of severe left testicular pain He had previously undergone left orchidopexy at the age of 6 years for an undescended testis On examination, the testis was tender, swollen and high in the scrotum At emergency exploration, the testis was found to have undergone torsion within an intact tunica vaginalis After derotation, the testis was viable It was returned to the scrotum and both testes were fixed. When the patient was seen at 7 weeks in the clinic, the testis was normal in size but a little tender

Patient 2

A 20-year-old man presented with sudden onset of pain in the left testis and groin He had previously undergone orchidopexy for an undescended left testis at the age of 16 years, when a reasonably sized testis had been brought down to a subdartos pouch. On examination, the left testis was tender and elevated, the epididymis appeared to face anteriorly Exploration revealed an intact tunica vaginalis and a 180° torsion of the testis After derotation the testis was viable Both testes were fixed

Discussion

The undescended testis is known to be at increased risk of torsion[1]. It is rare for a testis that has been brought down into the scrotum surgically to twist Only eight previous cases have been reported[2–6]. Torsion of a testis that has been operated on for other reasons and fixed has been described more frequently[3,7].

In the two patients presented, the tunica vaginalis was found to be intact at operation An intact tunica vaginalis was also found in three of the previously reported patients[3,6]. In one further case it was probably intact[6], although this is not entirely clear. In the remainder, no comment was made on the tunica. An intact tunica has been cited as a factor in torsion following orchidopexy[3]. This is perhaps not surprising, as it is the abnormal investment of the tunica that predisposes the testis to torsion[8] In standard accounts of orchidopexy for undescended testis, the step of everting the tunica vaginalis is not universal The present authors agree with a previous report[3], which states that this is an essential step in addressing the predisposition to torsion.

The use of absorbable sutures for fixation of the testis after torsion has been implicated in recurrence or subsequent contralateral torsion[7]. In the patients reported and reviewed here, catgut had been used in two cases (and probably in a third) for fixation at the original orchidopexy. In the remainder there was no record of the suture material; the use of an absorbable suture in these may have contributed to the subsequent torsion.

Torsion may occur in a testis that has previously undergone orchidopexy for failure of descent When performing orchidopexy, the tunica vaginalis should be everted and the testis should be fixed, preferably with a non-absorbable suture.

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Comparison of POSSUM with APACHE II for prediction of outcome from a surgical high-dependency unit

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POSSUM and APACHE II scores from 117 consecutive admissions to a high-dependency unit after major surgery were correlated with 30-day morbidity and mortality rates. Thirteen patients (11 per cent) died and 59 (50 per cent) developed a postoperative complication. Receiver–operating characteristic curve analysis showed POSSUM to have good predictive value for mortality (area under curve 0·75) and morbidity (area under curve 0·82). APACHE II scores had a significantly inferior predictive value for mortality (area under curve 0·54) ($P < 0{\cdot}002$)*. POSSUM was superior to APACHE II in prediction of mortality in patients admitted to a high-dependency unit after general surgery. Prediction of postoperative complications by POSSUM is accurate and may be useful for audit.*

Severity-of-illness indices have been developed and evaluated using postoperative death as the principal measure of outcome. Such indices are useful and superior to crude mortality statistics, but analysis of morbidity after surgery is not possible using available severity scores.

Previous work has concentrated on patients in an intensive care unit, where postoperative mortality and morbidity rates are expected to be high. The most widely used index, APACHE II (Acute Physiology and Chronic Health Evaluation)[1], was developed in a mixed group of medical and surgical patients. The percentage of postoperative patients contributing to the score was highly variable. APACHE II was not specifically designed for general surgical practice and its accuracy of mortality prediction has been disappointing in this specific group[2].

POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) accurately predicts overall mortality and morbidity rates after a wide range of general surgical procedures[3]. Most patients scored in the initial prospective study were predominantly of low risk, and the observed postoperative mortality rate (4·0 per cent) and complication rate (16·6 per cent) reflected this.

The general surgical high-dependency unit is a clinical area where general surgery and critical care overlap. In this study the accuracy of POSSUM and APACHE II for the prediction of outcome have been compared in a group of patients of predominantly higher risk admitted to the high-dependency unit after major general surgery.

Patients and methods

Patients

From January to June 1990, 255 patient admissions were recorded to the high-dependency unit. Analysis excluded 13 patients admitted with multiple injuries following trauma, 11 with medical conditions and 52 surgical patients admitted from the general ward or directly to the high-dependency unit with non-operative diagnoses. In all, 117 patients admitted to the unit immediately after surgery were available for study.

High-dependency unit

Clinical management on the high-dependency unit is directed by four general surgical consultants and the unit is permanently staffed by one surgical trainee on rotation. Care is provided by nurses trained in intensive care in a six-bed unit, with a nurse:patient ratio of 1:2. No patient receives mechanical ventilation. Anaesthetic input is available from the on-call team and intensive care consultant staff on request.

APACHE II and POSSUM scores

Patients were scored for APACHE II and POSSUM on admission to the high-dependency unit using physiological variables available immediately before surgery. This is normal practice for POSSUM, but deviates from the usual use of APACHE II, which takes the worst values available in the first 24 h after admission to the intensive care unit. Eleven patients had arterial blood gas analysis before operation; serum bicarbonate concentration was used as the alternative for the majority of APACHE II scores.

POSSUM requires scores from 12 physiological and six operative severity variables (*Table 1*) to estimate the risk of adverse postoperative outcome. Outcome risks (R) were calculated from logistic regression equations[3]. For postoperative morbidity the equation is:

$$\ln[R/(1-R)] = -5{\cdot}91 + (0{\cdot}16 \times \text{physiological score}) + (0{\cdot}19 \times \text{operative severity score})$$

For mortality the risk equation is:

$$\ln[R/(1-R)] = -7{\cdot}04 + (0{\cdot}13 \times \text{physiological score}) + (0{\cdot}16 \times \text{operative severity score})$$

For APACHE II the risk (R) of postoperative mortality was calculated using the equation[1]:

$$\ln[R/(1-R)] = -3{\cdot}517 + (0{\cdot}146 \times \text{APACHE II score}) + (0{\cdot}603 \text{ for emergencies}) + (\text{diagnostic category weighting})$$

Table 1 *POSSUM physiological and operative severity variables*

Physiological variables	Operative severity variables
Age (years)	Operation grade
Cardiac signs/chest radiograph	Multiple procedures
Respiratory signs/chest radiograph	Blood loss (ml)
Systolic blood pressure (mmHg)	Peritoneal soiling
Pulse rate	Malignancy
Glasgow Coma Score	Mode of surgery
Haemoglobin (g/dl)	
Leucocyte count ($\times 10^{12}$/l)	
Plasma urea (mmol/l)	
Plasma sodium (mmol/l)	
Plasma potassium (mmol/l)	
Electrocardiogram	

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Outcome

Death or complication up to 30 days after surgery was recorded for each patient Definitions and classification of morbidity are as previously described[3] and include haemorrhage, wound infection, deep infection, deep vein thrombosis, pulmonary embolism, and cardiac and respiratory failure

Statistical analysis

Risks derived from logistic regression equations were tabulated in ascending order for mortality and morbidity The total number of patients predicted to have an adverse outcome was calculated by successive addition of the number at risk multiplied by the percentage risk at 10-per cent intervals For each score, various decision criteria at 2 5-, 5- and 10-per cent incremental intervals were used to derive classification matrices, from which receiver–operating characteristic (ROC) curves were constructed The area under each curve was estimated using the method of Hanley and McNeil[4], by trapezoidal calculation of the Wilcoxon statistic (W) and its associated standard error (s e). Curve areas were compared using the method of Hanley and McNeil[5] by calculation of the critical ratio (z) for comparing two curves derived from the same patients. Frequency tables were compared using the χ^2 test

Results

The mean age of the 117 patients scored was 67 (range 21–96) years There were 54 men and 63 women.

Thirteen patients (11 per cent) died within 30 days of surgery A total of 70 postoperative complications were seen in 59 patients (50 per cent). These comprised chest infection (15 cases), wound infection (eight), cerebrovascular episode (five), arrhythmia (five), deep haemorrhage (four), myocardial infarction (four), cardiac failure (four), peritonitis (four), urinary tract infection (four), deep vein thrombosis (three), septicaemia (two), wound dehiscence (two), respiratory failure (two), oesophageal perforation (two), small bowel fistula (one), groin lymph leakage (one), pseudomembranous colitis (one), pulmonary embolus (one), hypotension (one) and graft occlusion (one)

The observed mortality and morbidity rates were not significantly different between patients admitted electively or as an emergency (*Table 2*). *Figure 1* shows mortality and morbidity distribution by age.

The postoperative mortality rate was highest in patients undergoing laparotomy for obstruction associated with disseminated intraperitoneal malignancy (*Table 3*) In patients undergoing vascular procedures, the mortality rate was highest (50 per cent) after major amputation.

The number of predicted deaths and complications compared with those observed is shown in *Table 4*. POSSUM predicted the crude incidence of complications accurately but overestimated the crude mortality rate compared with APACHE II *Figure 2* compares APACHE II and POSSUM mortality scores for each patient The predictive values of POSSUM and APACHE II were calculated using ROC curve

Table 2 *Incidence of mortality and morbidity according to presentation*

Presentation	No of patients	Mortality No	Mortality Rate (%)	Morbidity No	Morbidity Rate (%)
Elective	77	8	10	36	47
Emergency	40	5	12	23	58
Total	117	13	11	59	50

Table 3 *Incidence of morbidity and mortality according to operation*

Operation	No. of patients	Mortality No	Mortality Rate (%)	Morbidity No	Morbidity Rate (%)
Colorectal resection	44	2	5	22	50
Other GI resection	24	1	4	9	38
Malignant GI obstruction*	12	5	42	9	75
Renal or genitourinary	11	0	0	2	18
Vascular	26	5	19	17	65

GI, gastrointestinal. *Laparotomy for obstruction from malignant adhesions, no resection performed

Table 4 *Observed and predicted mortality and morbidity*

	Observed No	Observed Rate (%)	Predicted No	Predicted Rate (%)
Mortality				
POSSUM	13	11	20	17
APACHE II	13	11	10	9
Morbidity				
POSSUM	59	50	59	50

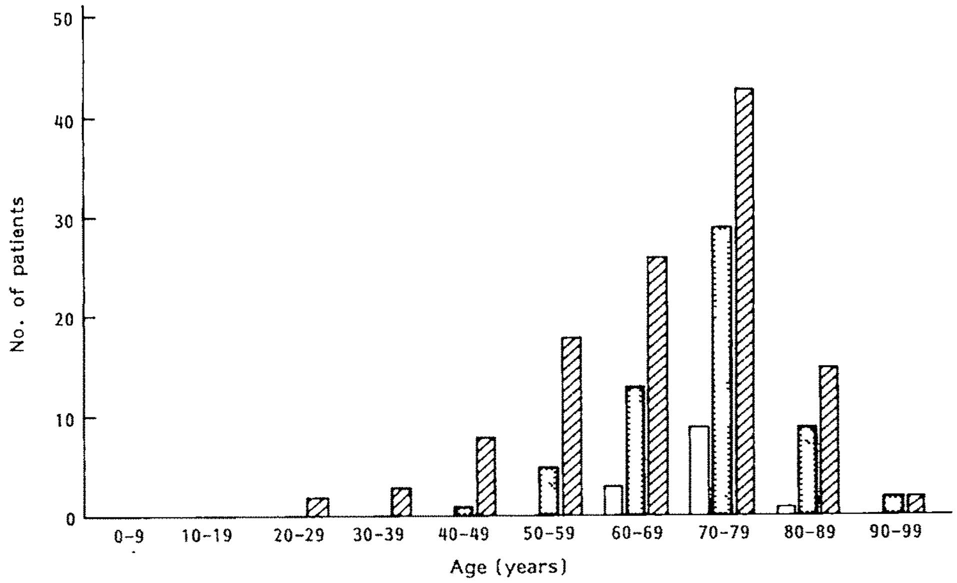

Figure 1 *Mortality (□), morbidity (⊓) and total patient numbers (■) according to age*

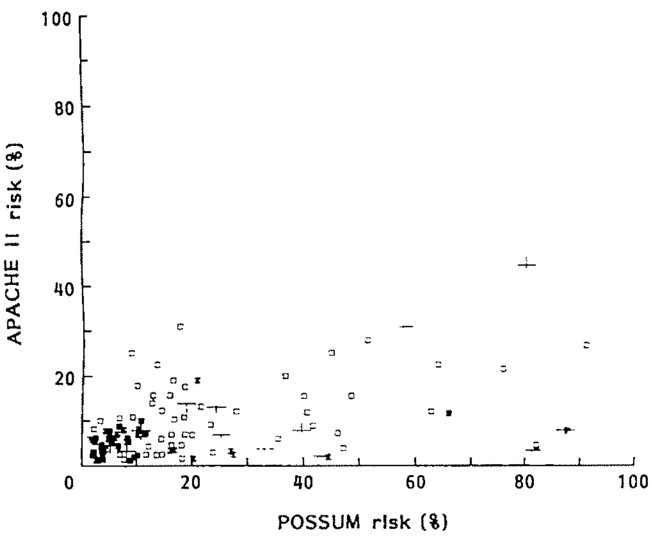

Figure 2 *Comparison of POSSUM and APACHE II estimated risks for mortality* □, *Survivors*, +, *deaths*

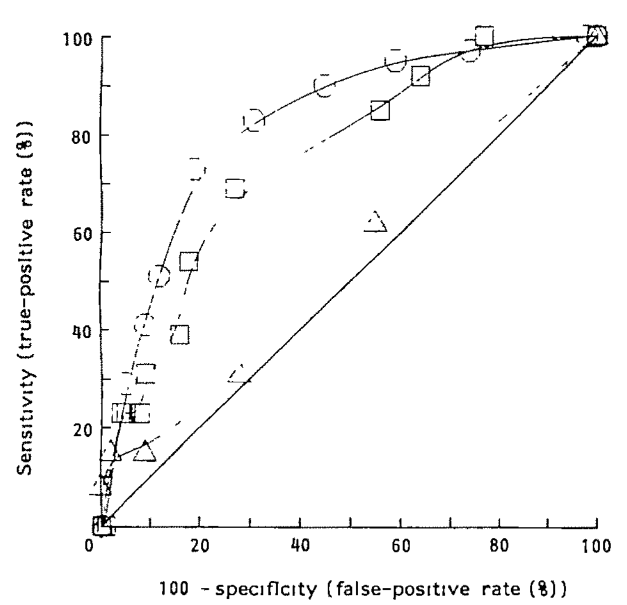

Figure 3 *Receiver-operating characteristic curves for mortality (POSSUM and APACHE II) and morbidity (POSSUM).* □, *POSSUM mortality,* △, *APACHE II mortality,* , *POSSUM morbidity,* —, *chance. Mortality area under curve POSSUM, 0 753, APACHE II, 0 539* (z = *2·95,* P < *0 002*)

analysis in which sensitivity and specificity at different cut-off points were plotted. Results are expressed as the area under the ROC curve (0·5–1·0) and its s.e. POSSUM was a good predictor of mortality (area(s e.) 0·753(0·081)) whereas APACHE II had poor predictive value with a ROC curve close to the line of chance (area(s e.) 0·539(0 083)) (*Figure 3*) The difference in curve area for mortality was highly significant (*z* = 2·95, *P* < 0·002).

Calculation of the ROC curve for morbidity (*Figure 3*) showed POSSUM to have good predictive value (area(s.e.) 0·823(0·039)) and a similar curve area to that derived from data from the original study[3] (area(s e.) 0 836(0·017)) It was not possible to compare POSSUM scores for morbidity with those for APACHE II as there is no equivalent odds ratio equation

Discussion

Crude mortality and morbidity data, collected for the purposes of audit, give a misleading impression of surgical performance[6]. POSSUM and APACHE II take account of physiological variation in patients and the severity of illness case-mix to compare outcome in large groups of patients.

The utilization of preoperative physiological values in the present study to derive APACHE II scores differs from normal practice. The present method has the advantage of comparing POSSUM and APACHE II scores derived from the same physiological values and is a measure of preoperative severity of illness. Scoring APACHE II after preoperative and peroperative resuscitative measures would improve each score and bias its comparison with POSSUM.

POSSUM predicted a higher mortality rate than that observed This decrease in observed mortality rate may be a reflection of postoperative high-dependency care, but is more likely to reflect a bias through selection Some patients at high risk would have been transferred to the intensive care unit and some not expected to survive would have been returned to the ward. The risk of postoperative morbidity would be less affected by such selection and the accuracy of prediction of morbidity matched that of the initial POSSUM evaluation.

APACHE II was not a useful predictor of mortality in this study In a smaller series, from a district general hospital surgical intensive care unit, APACHE II scores >22 had predictive value, although the sensitivity (30 per cent) was poor at this score. APACHE II was unreliable at scores[7] <22. APACHE II has been useful in predicting mortality from specific non-operative surgical conditions such as acute pancreatitis[8] and intra-abdominal sepsis[9]. It is apparent that the influence of severity of operation and peroperative resuscitation is not accounted for by this index, despite the diagnostic category weighting. The predictive ability of APACHE II after general surgery is consequently diminished, whereas POSSUM, which has the advantage of including operative severity variables, has a better overall predictive value.

Attempts have been made to extend the use of APACHE II to measure quality assurance and to limit costs by exclusion of very low- or very high-risk patients from intensive care admission[10]. For surgical patients this has not been a successful exercise[2], because exclusion from specialist treatment has the effect of increasing the risk of a poor postoperative outcome.

Audit of performance requires information other than that given by mortality rates[11]. The ability of POSSUM to predict morbidity and mortality rates has implications for audit of surgical performance and resource management as a whole. Many surgical units currently conduct mortality and morbidity review without assessment of expected risk. Inclusion of morbidity profiles into audit[12] may give insight into causes of postoperative morbidity but cannot audit performance between units or changes in the same unit with time. Calculation of resources should take account of the surgical case-mix and the expected morbidity rates from surgery.

POSSUM was superior to APACHE II for the prediction of postoperative mortality in a series of patients undergoing major general surgery in a high-dependency unit. The accuracy of prediction of postoperative complications in this high-risk group was as good as that predicted in a large series of low-risk patients[3] Further studies are in progress to assess the use of POSSUM in the intensive care setting and to evaluate the effects of resuscitation on the POSSUM score and subsequent outcome.

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Use of a modified Foley catheter for continuous irrigation of intra-abdominal abscess

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Intra-abdominal abscesses after surgical operations and trauma are still frequent, especially after operations or trauma to the gastrointestinal tract, liver, pancreas and spleen. Despite postoperative drainage, the tube used may become displaced or dislodged before its function is complete[1]. Subsequently, further oozing of blood or transudation of fluid within the abdomen occurs and does not drain adequately, and an abscess may form. A technique has been developed to handle such residual abscesses

Surgical technique

A 69-year-old man had an actively bleeding ulcer high in the body of the stomach He underwent total gastrectomy with Roux-en-Y oesophagojejunostomy Splenectomy was also performed because of operative injury, a sump drain was left in the splenic bed The volume of daily discharge was around 300–400 ml for the first 3 days, falling to 40–50 ml on subsequent days On the tenth day after operation, the patient began oral intake after radiological documentation of no leakage from either the oesophagojejunostomy or the closed end of the duodenum The sump drain became dislodged on the 13th day after operation and was reinserted However, the discharge gradually became scanty, turbid and with a foul odour Daily irrigation was performed but the situation remained unchanged Some 2 weeks later, the patient had fever and food was found in the discharge A barium meal under fluoroscopy disclosed a fistula at the blind end of the jejunum and an abscess cavity in the splenic bed A technique of continuously irrigating the abscess was developed to manage this drainage condition, and after 3 weeks of parenteral nutrition the effluent was clear and the tube was withdrawn

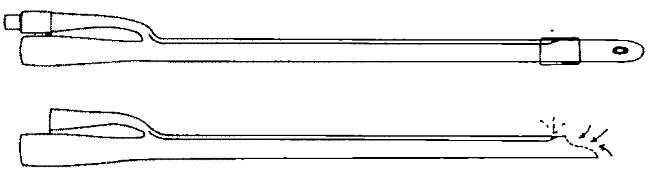

Figure 1 *The Foley catheter is modified by removing the balloon and trimming the catheter head half-concavely The air vent is transected and used as the entrance for irrigating fluid*

The irrigation technique developed is as follows The track of the original tube is repeatedly dilated by increasing the size of the drain daily Finally, a modified Foley catheter (24 Fr) designed as a closed irrigating device is inserted A daily volume of 1000 ml normal saline containing antibiotics in a bottle is then dripped in continuously by gravity through the air vent of the catheter The mixture of saline and pus flows out via the catheter without suction

The Foley catheter is modified as indicated in *Figure 1* The balloon is removed, taking care not to damage the inflation point, which will later be used for the influx of irrigating solution The head of the Foley catheter is cut and trimmed half-concavely This serves as the exit for the mixture of saline and pus If the cut end is horizontal to the catheter axis, sometimes the fluid will not be adequately collected and will leak outside along the Foley catheter The air vent of the catheter is transected and used for the entrance of irrigating fluid

Discussion

This technique has been used successfully to treat four patients including one after percutaneous drainage It is convenient, because various sizes of Foley catheter are always available and the method of modifying them is easy. Moreover, the closed system may avoid additional infection

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Autopsy analysis in surgical patients: a basis for clinical audit

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An autopsy study was performed to quantify diagnostic fallibility in clinical surgery. Autopsy results in 312 surgical patients were compared with clinical findings. The primary clinical diagnosis was correct in 93 per cent of patients; complications had been correctly diagnosed in 60 per cent and error in treatment was found in 16 per cent. Error in treatment had an adverse impact on the course of disease in 11 per cent of patients. Infective complications such as abdominal sepsis and bronchopneumonia were encountered most often. Sensitivity was low for the clinical diagnosis of pulmonary embolism, bronchopneumonia, myocardial infarction and terminal haemorrhage. Statistical analysis showed that sudden unexpected death is the most obvious condition in which a high yield is expected from a post-mortem examination. Autopsy remains a valuable means of quality control in clinical surgery and could be a basis for surgical audit.

Audit and quality control of clinical management are important in today's clinical practice. Autopsy as a contributor to surgical audit has been suggested by some[1–3].

In 1989, Anderson *et al.*[4] discussed the sensitivity and specificity of clinical diagnostics for a group of diseases of mainly medical origin. Autopsy data over a period of 50 years were compared and the issue of 'necessary fallibility' was introduced. Other studies have described discrepancies between clinical diagnosis and autopsy findings. It is postulated that there is an irreducible error rate inherent in the diagnostic process, at least that of patients dying in hospital[5–7]; error rates detected by autopsy can be as high as 20–30 per cent for hospital patients[8,9]. In this era of declining autopsy rates, any instance of missed clinical diagnosis that had an adverse impact on the course of the disease may be quickly forgotten

This study assesses the value of autopsy as a means of quality control in surgical patients. It deals with the sensitivity and specificity of clinical diagnosis assessed using autopsy findings.

Patients and methods

During the period 1977–1987 an autopsy was requested for every patient who died in the department of general and vascular surgery at Nijmegen University Hospital. During this period the department had 3000–3500 admissions and was performing 2500–3000 operations annually. Consent from relatives was obtained in 312 cases The mean annual autopsy rate over this period was 51 (range 36–62) per cent Instances in which relatives refused consent were not included in this series No surgery was carried out in 48 patients The clinical notes were compared with post-mortem findings and any discrepancies discussed with a senior surgeon and pathologist Differences between descriptive clinical terms and morphological autopsy diagnoses were noted only in cases of clear discrepancy; trivial inaccuracies were not scored.

The accuracy of the primary surgical diagnosis, the diagnosis of complications and relevant contributory diagnosis were assessed. False-negative and false-positive results were counted and sensitivity and specificity calculated for a range of diagnoses

Treatment and diagnostic procedures were evaluated and compared with post-mortem findings A number of factors were statistically analysed to detect any influence on accuracy of diagnosis or treatment Statistical analysis used the χ^2 test for unpaired data

Results

The 312 patients comprised 198 male and 114 female, of mean age 60·0 (range 14–93) years. Patients were divided into five subgroups according to the main clinical diagnosis: (1) 77 patients with malignant tumour, (2) 56 suffering trauma; (3) 68 with vascular disease requiring surgery; (4) 77 with benign digestive tract disease needing operation; and (5) 34 with other miscellaneous diagnoses. The prognosis on admission was fairly good for 77 patients, poor for 140 and unclear for 95

Treatment was withheld in the terminal phase of disease in 33 patients with a poor prognosis on admission without any failure in management according to post-mortem analysis.

Twelve patients died during surgery; 160 died on the surgical intensive care unit and a further 38 had been admitted to this unit during their hospital stay. Twenty-six patients died within 24 h of admission. Patients were admitted for emergency procedures in 182 cases and electively in 130.

Clinical diagnosis

According to autopsy analysis the clinical diagnosis was correct throughout in 159 patients (51 per cent) although, despite a correct diagnosis, treatment had been incorrect in 12 of these cases.

The primary clinical diagnosis was correct in 290 patients (93 per cent) and complications of the primary disorder or its treatment were correctly diagnosed in 188 (60 per cent); error occurred in diagnosis of complications in 124 patients, and was relevant to the course of the disease or its treatment in 34.

The direct mechanism of death was correctly diagnosed in 247 patients (79 per cent) Sudden unexpected death occurred in 44 patients but the cause was accurately diagnosed in only 22. Death from brain damage occurred in 18 patients, from direct trauma in 15 Brain damage as the direct cause of death was missed in two patients (diagnostic sensitivity 89 per cent).

Relevant contributory diagnoses, unrelated to the primary disorder or its complications, were diagnosed correctly in 296 patients (95 per cent).

Diagnostic procedures

According to post-mortem assessment, diagnostic procedures were correct in 282 patients (90 per cent). The results were helpful in 270 of these patients but misleading in 12 Diagnostic procedures had been inadequate in 30 patients (10 per cent). Diagnostic errors occurred in 15 patients with abdominal sepsis: these included nine cases of failure to perform ultrasonography for localized collections of pus and six failures to perform exploratory (re)laparotomy for free bowel perforation (without localized pus collection). Diagnostic errors also occurred in 15 patients without abdominal sepsis: three with pulmonary embolism did not undergo scintigraphic examination; three had chest disorders but chest radiographs

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Table 1 *Treatment errors in 312 surgical patients*

Failure to treat abdominal sepsis by (re)laparotomy	17
Failure to treat abdominal bleeding by (re)laparotomy	9
Failure to perform other surgical operations	9
Non-surgical errors	16
Total	51

were not taken; three had cardiovascular disorders that could have been diagnosed by ultrasonography; two had severe haemorrhage in whom time was lost trying to perform angiography; three had insufficient laboratory investigations, and one underwent an insufficient physical examination.

Errors of treatment

Comparison of clinical notes with autopsy findings showed that treatment had been incorrect in 51 patients (16 per cent), of whom 12 had correct diagnoses. The error in treatment had had a clearly adverse effect on the course of disease in 35 patients (11 per cent), and had been likely to be adverse in 16 (5 per cent). The treatment errors that occurred most frequently are shown in *Table 1*.

Complications

Abdominal sepsis occurred in 94 patients and was most often found in those with benign gastrointestinal disease. In 11 patients the diagnosis was missed completely (inadequate diagnostic procedures in 15 cases) in the clinical phase, giving a sensitivity of 88 per cent Correctly performed diagnostic procedures but with misleading results occurred in four patients with abdominal sepsis: one false-negative ultrasonographic examination; one false-negative laparotomy (duodenal perforation); one false-negative plain radiograph; and one false-negative biopsy of pancreatic cancer. Multiple organ failure was associated with abdominal sepsis in 38 patients

A leaking intestinal or gastric anastomosis was found as a complication in 29 patients and three were missed clinically, giving a sensitivity of 90 per cent. The specificity was 100 per cent

Bronchopneumonia was found at autopsy in 142 patients. The diagnosis had been missed clinically in 37 and six false-positive diagnoses occurred, giving a sensitivity of 74 per cent and specificity of 96 per cent. Bronchopneumonia was a common disorder in all subgroups and was missed equally in all, often as a late complication in severe illness.

Multiple organ failure was found to be associated with bronchopneumonia in 43 patients, of whom 24 also had abdominal sepsis.

Pulmonary embolism was found at autopsy in 21 patients and had been missed clinically in 15, a sensitivity of 29 per cent False-positive diagnoses were seen 11 times (specificity 96 per cent). Pulmonary embolism was most frequently found in patients with malignant disorders, but was often missed in all subgroups.

Myocardial infarction was present in 36 patients at autopsy. Ten cases were missed clinically and 13 false-positives occurred, a sensitivity of 72 per cent and specificity of 96 per cent Myocardial infarction was found most often in the group of patients with vascular disorders.

Haemorrhage occurred as the direct mechanism of death in 52 patients and was detected clinically in 39. Two false-positive diagnoses occurred (sensitivity 75 per cent, specificity 99 per cent) Terminal haemorrhage occurred most frequently in patients with vascular disorders

No significant differences in diagnostic sensitivity or specificity for the above complications were found for any of the five subgroups.

Statistical analysis

Relevant factors that might influence the accuracy of diagnosis or treatment were sought. Sudden death ($\chi^2 = 12\cdot68$, 1 d.f., $P < 0\cdot001$) and failed diagnostic procedures ($\chi^2 = 29\cdot60$, 2 d.f., $P < 0\cdot001$) were significantly associated with incorrect clinical diagnosis Significantly associated with incorrect treatment were sudden death ($\chi^2 = 13\cdot41$, 1 d.f., $P < 0\cdot001$), failed diagnostic procedures ($\chi^2 = 70\cdot09$, 2 d.f., $P < 0\cdot001$) and the occurrence of an iatrogenic complication ($\chi^2 = 6\cdot67$, 1 d.f., $P = 0\cdot01$).

Death from cerebral damage or involving abstention from treatment in the terminal phase of disease were significantly associated with correct therapy ($\chi^2 = 3\cdot95$, 1 d.f, $P = 0\cdot05$ and $\chi^2 = 8\cdot20$, 1 d.f, $P = 0\cdot004$ respectively).

Analysis did not show any significant influence on accuracy of diagnosis or treatment for age, sex, length of hospital stay, time between admission and operation and year of death. Elective or emergency admission influenced the accuracy of neither diagnosis nor treatment. No correlation was found between incorrect diagnosis or treatment and any specific primary surgical disorder or complication

Statistical analysis showed that in the 48 patients who did not undergo surgery diagnostic and therapeutic accuracy were equal to those in patients undergoing operation.

Discussion

Discrepancies between clinical and post-mortem diagnoses describe error rates of 30–40 per cent, with decisions affecting survival in up to 10 per cent of patients[8–11].

The present study shows that clinical accuracy in surgical patients is not much higher than in previous studies of non-selected hospital deaths. The greatest number of errors occurred in the assessment of complications.

Pulmonary embolism was found to be as difficult to diagnose in the present patients as in other studies[6,8,11–13] Bell and Zuidema[14] found that 15 per cent of postoperative deaths were caused by pulmonary embolism. A 30-year survey by Bergqvist and Lindblad[15] showed that pulmonary embolism was found at autopsy in 23 per cent of deaths in surgical patients. The incidence and case fatality rate for pulmonary embolism in the hospital population have decreased recently[15,16], and this is demonstrated by the absolute number in the present study.

Septic conditions are a major cause of morbidity in older patients and in those in intensive care units[5,17–19]. Multiple organ failure is frequently associated with sepsis[20]. The most important error of treatment detected was failure to undertake (re)laparotomy in patients with abdominal sepsis. Diagnosis is difficult if there is multiple organ failure. Ultrasonography is easily performed and only one false-negative result was found in the present study.

A number of instances occurred in which localized bleeding may have been treatable.

The cause of sudden unexpected death is often misdiagnosed[12,21] and myocardial infarction should be suspected in this situation in both hospital and non-hospital patients.

Anderson *et al.*[22] reported that diseases with a low prevalence were most likely to be missed clinically, but this was not confirmed in the present study of surgical disorders.

Patients beyond treatment, those dying from brain damage or in whom treatment was withheld in the terminal phase, were not affected by errors in management.

Accuracy rates have been described as being influenced by age[7,11,17,22–25] or by the duration of hospital stay[11,26]. Most studies indicate that diagnosis is more frequently incorrect for elderly than for young patients and that prolonged hospital stay may lead to overdiagnosis. Fernandez-Segoviano *et al.*[27] found no relationship between the accuracy of diagnosis and length of stay in an intensive care unit. The present study supports their observation.

This analysis shows that selection of cases for autopsy is not likely to improve the management of surgical patients. The errors described in diagnosis and treatment did not originate from malpractice or negligence. The concept of 'necessary fallibility' should be embraced by surgeons to aid their understanding of the pathophysiology of surgical disorders and their complications. Autopsy should serve as a method of quality control to define the limits of permissible error rates.

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Circadian variation in unexpected postoperative death

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Unexpected deaths still occur following major surgical procedures. The cause is often unknown but may be cardiac or thromboembolic in nature. Postoperative ischaemia, infarction and sudden cardiac death may be triggered by episodic or constant arterial hypoxaemia, which increases during the night. This study examined the circadian variation of sudden unexpected death following abdominal surgery between 1985 and 1989 inclusive. Deaths were divided into those occurring during the day (08.00–16.00 hours), evening (16.00–24.00 hours) and night (24.00–08.00 hours). Twenty-three deaths were considered to have been totally unexpected. Of 16 such patients undergoing autopsy, pulmonary embolism was the cause of death in five. In the remaining 11 patients, death occurred at night in eight ($P < 0\cdot005$*). Five of the seven patients without an autopsy died at night (*$P < 0\cdot04$*); overall, 13 of 18 unexpected deaths occurred at night-time. These results suggest a need for further studies of sleep- and respiration-related effects on postoperative nocturnal cardiac function. The efficacy of monitoring during this apparent high-risk period should be evaluated.*

Major surgery is still associated with significant morbidity and mortality[1,2]. Periodicity occurs for time of death in the general population not undergoing surgery[3–5], time of onset of chest pain in acute myocardial infarction[6–8], time of transient myocardial ischaemia in patients with coronary artery disease[9,10], time of onset of ischaemic stroke[11] and of attacks of asthma[12–14]. Nocturnal severe episodic or constant hypoxaemia is common late after operation, with episodic hypoxaemia being observed predominantly during sleep[15–17]. The clinical implications of late postoperative low oxygen saturation are not known, but when episodic it may be associated with cardiac ischaemia and arrhythmia[16], and may represent an important factor in the development of late postoperative myocardial infarction[18] and sudden death. This study examined the circadian variation in unexpected postoperative death.

Patients and methods

All deaths within the first week after surgery during the 5-year period from 1985 to 1989 were reviewed. In this period all patients over 40 years of age received prophylactic low-dose heparin and elastic stockings to prevent pulmonary embolism.

Deaths were divided into those during the day (08.00–16.00 hours), evening (16.00–24.00 hours) and night (24.00–08.00 hours). Because many deaths occurred in patients with potentially life-threatening complications, a selection procedure (*Figure 1*) was used to find postoperative deaths where no explanatory pathology could be identified. The exclusion of patients with potentially life-threatening complications after operation was performed from the records by a senior doctor with no knowledge of the time of death.

For statistical analyses the non-parametric sign test[19] was used. To overcome the problem of mass-significance and the time factor (night lasts 8 h, day and evening 16 h), tests were performed for day- and evening-deaths *versus* twice the recorded number of night-deaths. $P < 0\cdot05$ was considered significant.

Results

A total of 744 deaths occurred: 241 during the day, 236 in the evening and 267 at night (P not significant). Of the 744 deaths only 59 were both unexpected and occurred within 7 days of surgery. The majority (627 patients) had either had no surgery or received high-dose morphine infusion for alleviation of pain from terminal cancer (*Figure 1*). Fifty-eight patients died >7 days after surgery. Of the 59 deaths remaining for further analysis, 18 patients were considered to have suffered from early postoperative life-threatening complications such as shock, heart failure and the sepsis syndrome. Another 18 patients suffered late postoperative (>4 h after surgery) potentially life-threatening complications such as cardiac arrhythmia, stroke and severe pulmonary dysfunction requiring oxygen therapy or artificial ventilation. Thus, 23 deaths were considered to have been sudden and totally unexpected (*Figure 1*); a typical statement in the patient's file was 'found dead in bed'. In these 23 patients the median age was 74 (range 48–86) years, ten were men. Eight had preoperative cardiac or pulmonary disease requiring regular medication and 15 underwent surgery for an acute problem.

Of 16 patients undergoing autopsy, pulmonary embolism was the cause of death in five. In the remaining 11 patients, death occurred at night in eight ($P < 0\cdot005$). In the seven patients without autopsy, five deaths occurred during the night ($P < 0\cdot04$). Thirteen of 18 unexpected deaths occurred during one-third of the day (24.00–08.00 hours) ($P < 0\cdot0003$). The circadian variation in unexpected postoperative death and the distribution of unexpected deaths in the first week after surgery are shown in *Figure 2*.

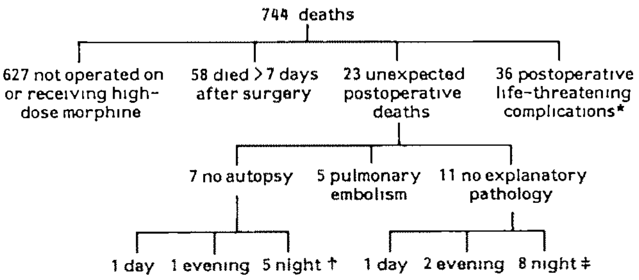
744 deaths
627 not operated on or receiving high-dose morphine
58 died >7 days after surgery
23 unexpected postoperative deaths
36 postoperative life-threatening complications*
7 no autopsy
5 pulmonary embolism
11 no explanatory pathology
1 day
1 evening
5 night †
1 day
2 evening
8 night ‡

Figure 1 *Selection procedure in the analysis of deaths during a 5-year period.* * *Life-threatening complications presumably influencing time of death* †$P < 0\cdot04$, ‡$P < 0\cdot005$ (*day- plus evening-deaths* versus *twice number of night-deaths, sign test*)

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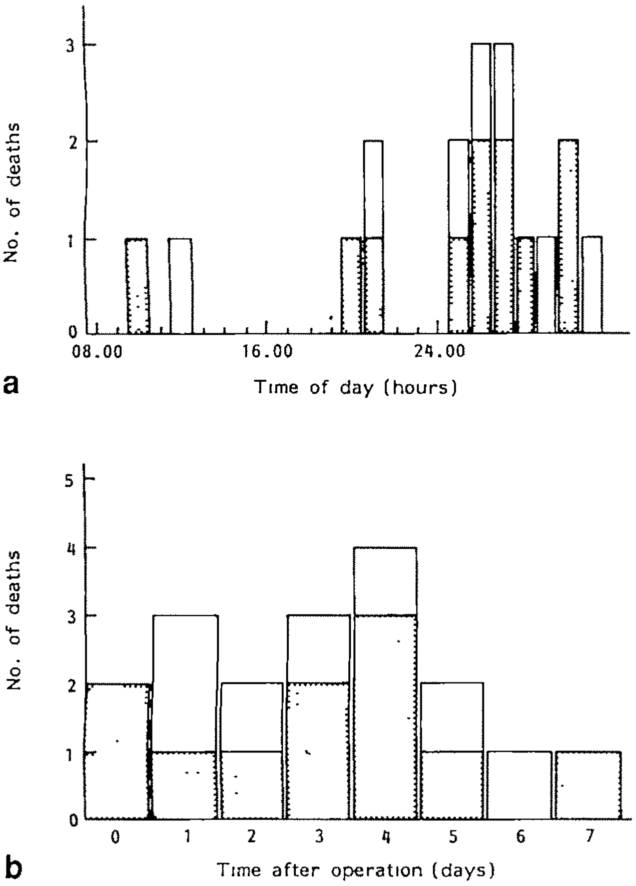

Figure 2 **a** *Circadian variation in unexpected postoperative death and* **b** *distribution of unexpected deaths in the first week after operation in the 11 patients with autopsy* (▨) *and the seven without* (☐) *in whom death could not be explained*

Discussion

This study demonstrates significant circadian variation in the frequency of sudden unexpected postoperative death. Compiled data for 437 511 non-surgical patients have previously shown that a major peak of deaths occurs between 04.00 and 06.00 hours regardless of cause[3]. The subgroup of sudden cardiac death seems to occur between 07.00 and 11.00 hours[4,5]. Occurrence of acute myocardial infarction determined by the onset of chest pain is most likely to occur between 06.00 and 13.00 hours, with a peak incidence at 09.00 hours[6], or between 06.00 and 09.00 hours with an additional peak at 24.00 hours[7]. The morning peaks may be caused partly by an increase in platelet aggregability[8]. The time of transient myocardial ischaemia in patients with coronary artery disease shows the same trend as the onset of acute myocardial infarction, with peak incidences at 06.00–10.00 hours[9] and 08.00–13.00 hours[10]. Onset of ischaemic stroke also shows a peak incidence in the morning between 10.00 and 12.00 hours[11]. In some asthmatic subjects sleep may be a contributing factor in the worsening of bronchoconstriction[12], which leads to an increased number of asthmatic deaths at night[13,14].

Several mechanisms of sudden unexpected death in the present study are possible. Unexpected fatal pulmonary embolism was found in five patients; in the remaining deaths cardiac infarction or arrhythmia is most probably the pathogenetic factor. The majority of postoperative myocardial infarctions (50–70 per cent) and ischaemic episodes (94 per cent) are silent[20]. Repeated episodes of ischaemia may have a cumulative effect and eventually cause myocardial infarction[21], and postoperative ischaemia may be associated with adverse cardiac outcome such as myocardial infarction and sudden death[22,23]. A number of factors may be involved in the development of cardiac ischaemia, such as constant postoperative tachycardia induced by pain and surgical stress[16,24], disruption of fluid and electrolyte homoeostasis[25], and arterial hypoxaemia[16,18,26,27]. Episodes of arterial hypoxaemia may be harmful for the heart[16,18,26], since they are often accompanied by rises in pulse rate[15,16,26] and blood pressure[28,29], leading to a marked increase in the rate–pressure product. Severe episodic changes in arterial oxygen saturation are especially seen in the sleep apnoea syndrome that may prove to be an important surgical risk factor[28,30,31]. The prevalence of this syndrome in the surgical population is unknown, but may be as high as 10 per cent, especially in old age[32]. Lying supine, as in the postoperative period because of pain, aggravates the ventilatory disturbance with pronounced apnoea and worsened episodic oxygen desaturation[33]. Snoring is associated with considerable morbidity and mortality[29,34–36], and patients with obstructive sleep apnoea are more likely to die during sleep[37]. An undiagnosed sleep apnoea syndrome could thus have been a contributing pathogenetic factor in some of the present patients with sudden postoperative death.

Patients with obvious or possible causes of death were excluded from analysis to allow an examination of deaths in the light of unopposed postoperative hypoxaemia and sleep-related cardiopulmonary problems. These were less likely to occur beyond the first week after surgery[38–40]. The 36 patients so excluded in *Figure 1* may have been affected by an unexpected cardiac event that could have been attributed to postoperative hypoxaemia and/or sleep-related cardiopulmonary problems, but because they had several competing severe organ dysfunctions it was impossible to determine the exact cause of death or time of occurrence of the initial event leading to complications and death.

It may be argued that the events leading to unexpected death would have been discovered and successfully treated if the patients had been monitored more intensely, especially during the night. Routine nocturnal surveillance late after operation in the majority of surgical departments is by hourly checks by a nurse usually recording whether the patient is breathing or not. In the light of the present results and recent studies demonstrating severe nocturnal hypoxaemia and related cardiac events[15,16,26], routine monitoring with pulse oximetry or continuous electrocardiography may be indicated for several days after surgery.

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Traumatic amputation by explosive blast: pattern of injury in survivors

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Explosive blast causes a pattern of injury including primary blast lung, secondary fragment injury and traumatic amputation of limbs. Major traumatic amputation is rare in survivors of bomb blast but common in those who die. The mechanism of such injury has not been previously determined, but must be established if protective measures are to be developed for members of the armed forces. The nature of 41 traumatic amputations in 29 servicemen who survived to reach medical care after blast injury was investigated to determine the anatomical level of amputation and the pattern of soft tissue damage. Joints were an infrequent site of amputation and the tibial tuberosity was a particularly frequent site of lower-limb severance. Comparison of the pattern of injury was made with that seen in ejecting fast-jet pilots, who frequently suffer major flailing injury; there appears to be a substantially different injury distribution. The accepted mechanism of traumatic amputation, avulsion by the dynamic overpressure, is challenged; it is suggested that the shockwave resulting from an explosion is capable of causing at least bone disruption in a limb.

Exposure to explosive blast results in a well documented pattern of injury[1,2]. The components of blast that cause injury are the shockwave, with its sharp leading edge of almost instantaneous pressure rise from ambient air pressure to the overpressure created by the explosion (shock front), and the dynamic overpressure or blast wind, which is the mass movement of the gaseous products of detonation away from the point of explosion. The shockwave is responsible for primary blast injury (blast lung, tympanic membrane rupture), and the dynamic overpressure for secondary (fragment) injury and tertiary injury (traumatic amputation and displacement of the body as a whole). The most frequent cause of injury is penetration by secondary missiles accelerated away from the point of the explosion by the dynamic overpressure; the majority of injuries sustained by survivors of blast are of this variety.

Primary blast injury and traumatic amputation of limbs are rarely found in survivors. It would seem that, if close enough to an explosion to suffer major traumatic amputation, the victim is highly likely to sustain associated injuries that prove fatal. Reviews of large numbers of casualties of bomb blast indicate that traumatic amputation is seen in only 1–2 per cent of those who survive to reach medical care[3,4] and that traumatic amputation in a casualty is highly suggestive of other serious injury. This low incidence of amputation in survivors of bomb blast contrasts markedly with the incidence of such injury in fatalities. Hill's series[5] of 305 fatalities from bomb blast in Northern Ireland from 1969 to 1977 showed a high incidence of traumatic amputation, with 15 per cent of victims having sustained lower-limb severance at or below knee level.

This study of the pattern of injury in survivors of exposure to explosive blast looks in detail at the injuries sustained by members of the armed forces in the past 12 years. In 29 servicemen identified, 12 amputations were caused by detonation of small antipersonnel mines in the Falkland Islands campaign. The mechanism of injury from mines is well documented[6–8] and these amputations have not been studied, other than to confirm that all appeared to be typical forefoot and heel disruptions tending to incapacitate rather than kill. Although some antipersonnel mines are considerably more powerful than those used in the Falklands and are capable of causing major traumatic amputations and death, there were no injuries from these in the present series. It may be that antipersonnel mines are a special case and that contact exposure to relatively small explosive charges produces a different pattern of injury than the larger, more remote, overpressures often encountered in terrorist and accidental bombings. The present series has, however, included injuries caused by land mines (antitank mines).

Patients and methods

The case notes, including field medical record cards where appropriate, of 29 servicemen who survived exposure to explosive blast between 1979 and 1990 and who suffered major traumatic amputation(s) were studied. Major amputations were considered to be all those that occurred at or above the wrist or ankle. Amputations caused by antipersonnel mines were excluded for the reasons given. In all cases, the site of the initial traumatic amputation caused by the blast was of primary interest, rather than that of subsequent elective surgical amputation. The precise level of traumatic amputation and associated soft tissue injury was often incompletely recorded in field medical documents.

Results

Source of blast

A variety of explosive devices were responsible for the injuries (*Table 1*). In only four cases was the patient known to have

Table 1 *Source of explosive blast causing traumatic amputation*

Source of explosion	No. of amputations
Air-dropped bomb or missile	14
Mortar or grenade	5
Land mine (antitank)	8
Car bomb	5
Booby trap or improvised explosive device	5
Detonation cord or plastic explosive	3
Aircraft tyre explosion	1
Total	41

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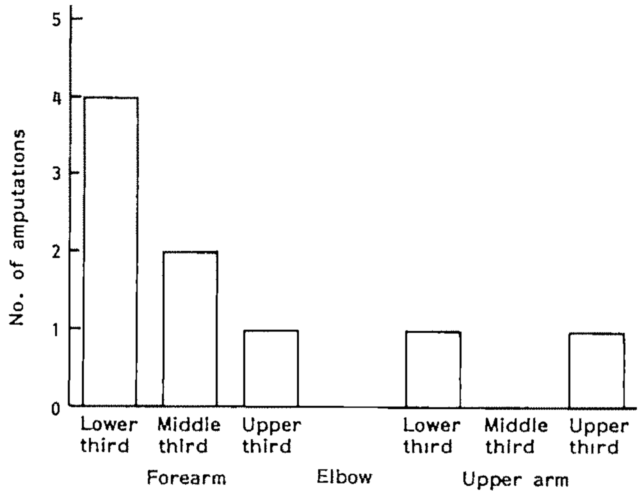

Figure 1 *Site of nine traumatic upper-limb amputations*

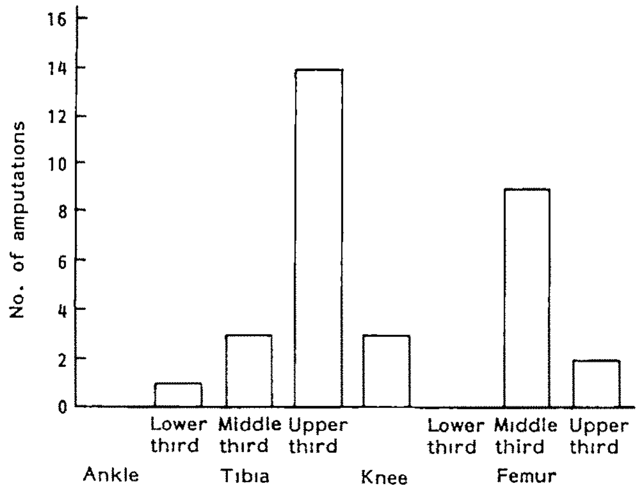

Figure 2 *Site of 32 traumatic lower-limb amputations*

been in physical contact with the device; distances of the casualties from the point of explosion and their orientation were not recorded. The exact placement of devices such as car bombs was also not identified. Any assessment of approximate blast overpressure acting on the injured is therefore impossible, despite the availability of accurate information concerning the type and weight of the charges in many instances. No traumatic amputations in this series were caused by exploding artillery shells.

Level of amputation

Upper limb. A total of nine traumatic amputations at or above wrist level were identified in eight casualties (*Figure 1*). Although numbers were small, a tendency for amputation to occur through the distal portion of the limb was identified.

Lower limb *Figure 2* shows the location of 32 lower-limb amputations in 21 casualties. By excluding direct-contact traumatic amputation from antipersonnel mines, it was seen that the tibial tuberosity was the prime site of severance ($\chi^2 = 43$, 8 d.f, $P < 0{\cdot}001$). Only a small number of amputations occurred through the knee joint, a likely area of weakness. The apparent peak in the middle third of the femur may be accounted for by generalization in recording of the level of amputation by those who completed the medical records In several cases, medical notes specified only that the amputation was above-knee; these have been grouped in the middle-third category.

Soft tissue injury and formal amputation

Fragmentation of the explosive device produced significant secondary missile injury in several cases, especially to the contralateral limb. Damage to the soft tissues proximal to the level of amputation was extremely difficult to ascertain: the medical notes seldom mentioned the degree of soft tissue injury, and the macroscopic appearances of the skin and muscle were rarely recorded in detail

Comparison of the level of traumatic severance with that of initial surgical debridement or of formal amputation offers a crude indicator of the soft tissue injury at the primary traumatic amputation site It is accepted that in some instances formal amputation was sited more proximally than absolutely necessary so as to accommodate a subsequent prosthesis. Using the same units of level as described in *Figures 1* and *2* (lower third, middle third, etc.), it was calculated that formal amputation was carried out for 17 injuries at a mean level 1·47 units above that of the traumatic amputation. The range of this figure was 0–3, formal amputation being performed at three levels higher in one case where severe fragment injury, causing gross soft tissue damage, complicated the traumatic amputation. Most below-knee amputations passing through the tibial tuberosity resulted in above-knee formal stumps, sited at the level of the lower femur.

Associated injuries

Table 2 details the injuries associated with the traumatic amputations, where known. Secondary fragmentation was responsible for a considerable number of serious injuries, and weapons designed to generate secondary fragments produced a higher incidence of this form of associated trauma. Primary blast injury to the ear and lung was only rarely recorded, but it is probable that tympanic membrane rupture occurred in the majority of casualties notwithstanding the lack of reference to the injury in medical documents Primary blast lung is extremely rare in survivors of explosion[5] and only one casualty had the diagnosis suspected on clinical grounds. He made an uncomplicated recovery and initial hypoxia resolved over 24 h.

Discussion

This review of the pattern of traumatic amputation in service survivors of bomb blast is hampered by lack of detail recorded in medical notes This is inevitable, as in many cases the hostile environment at the time of injury would have been less than conducive to accurate and detailed description of severe and life-threatening trauma. There are relatively few cases in the study, which confirms that traumatic amputation is rare in survivors of bomb blast.

A wide range of explosive devices were responsible for the amputations in this series Charge weights varying from about 1 kg in the case of booby traps in Northern Ireland to air-dropped bombs and antiship missiles (Exocet) with explosive warheads of >50 kg in the Falklands War make comparison of injuries difficult. In all cases, however, it is reasonable to assume that, whatever the size of the explosive device, there were sufficient blast effects acting on the casualty to cause traumatic amputation without rendering associated fatal injuries. It is also very difficult to differentiate between explosions giving a high yield of primary and secondary fragments and those creating relatively few. Hand grenades and mortars are designed to produce multiple fragments; the majority of terrorist bombs, booby traps and improvised explosive devices are not. The frequency of associated penetrating injuries to body areas remote from the site of amputation does, however, give some guidance to the quantity of fragments produced by a particular explosion.

The small number of upper-limb amputations prevents any significant conclusions being drawn, other than to suggest that the lower forearm appears more vulnerable than any other site in the limb. It is possible that, because of the relative proximity of the upper limbs to the trunk and head, a blast sufficient to

Table 2 *Details of 41 traumatic amputations, responsible devices and associated injuries in 29 casualties*

Injury	Traumatic amputation	Cause	Associated injuries
Upper limb			
1	Upper-third forearm	Exocet	Fragment wounds to abdominal wall and legs
2	Lower-third arm	Bomb	None recorded
3	Lower-third forearm	Booby trap	Fractures of right hand, flash burns
4	Lower-third forearm	700 g plastic explosive	Fragment wound to right leg, bilateral PTM
5	Lower-third forearm	Detonation cord	Small bowel perforation, burns to thighs, ruptured testis, bilateral PTM
6	Lower-third forearm		
7	Mid-third forearm	Grenade	Fragment wounds to abdomen and right leg, large and small bowel perforation, bilateral PTM
8	Mid-forearm	Tyre explosion	Fractures of left hand
9	Upper-third arm	Air-dropped bomb	None recorded
Lower limb			
10	Upper-third tibia	Bomb	None recorded
11	Upper-third tibia	Mine	Severe head injury, partial amputation of right arm
12	Upper-third tibia		
13	Upper-third tibia	Rocket	Burns to face and right hand
14	Upper-third tibia		
15	Mid-femur	Mortar	Fragment wound to right leg
16	Upper-third tibia	Mortar	Fragment wounds to left leg
17	Upper-third femur	Sidewinder	Fragment wound to right calf
18	Mid-tibia	Sidewinder	None recorded
19	Lower-third tibia		
20	Through-knee	Sidewinder	Avulsion of left testis
21	Upper-third tibia	Mortar	Gunshot wound to left calf
22	Mid-third femur	Car bomb	Fragment wounds to right arm and trunk, fractures of right hand, PTM
23	Upper-third tibia	Booby trap	Fragment wounds to both legs, PTM, ?blast lung
24	Upper-third tibia	Mine	Fractured mandible
25	Through-knee		
26	Upper-third tibia	Mine	Fractures and fragment wounds to left hand
27	Upper-third tibia		
28	Upper-third tibia	Mine	Lacerations to liver
29	Upper-third tibia		
30	Upper-third femur	IED	Enucleation of right eye, fragment wounds to right arm and trunk, bilateral PTM
31	Mid-third tibia		
32	Mid-femur	Exocet	Fragment wounds to scalp, abdominal wall, chest and arms
33	Through-knee		
34	Mid-femur	Car bomb	Not known
35	Mid-femur		
36	Mid-femur	Car bomb	Not known
37	Mid-femur		
38	Mid-tibia	Sidewinder	Not known
39	Upper-third tibia	Bomb	Not known
40	Mid-femur	Grenade	Not known
41	Mid-femur		

IED, improvised explosive device, PTM, perforated tympanic membrane Exocet is an antiship missile, warhead size >50 kg, Sidewinder is an antiaircraft missile, warhead size >30 kg (exact size classified)

cause traumatic upper-limb amputation is more likely to inflict other fatal injuries than one directed at the lower limbs. The majority of upper-limb amputations may therefore have occurred in casualties excluded from this study by their failure to survive to reach medical care.

Lower-limb amputations caused by explosive blast show a significant tendency to be through the upper third of the tibia, in the region of the tibial tuberosity. It is also notable that the ankle and knee joints are not sites of frequent limb failure (three cases), although they are potential areas of weakness That joints are usually spared in these injuries will not surprise surgeons with experience in this field The distribution of amputations in this series agrees well with that of Calderwood, who looked at bomb blast injuries in Northern Ireland[9]. In that series, four of 12 amputations were below-knee and only one passed through a joint.

The degree of soft tissue damage around the site of traumatic amputation cannot be reliably assessed from the medical notes of the subjects in the present study. That surgical amputation occurred in the majority of cases at one or two levels above that of the traumatic damage is a rough indication of the destruction of the soft tissues, but in many cases formal amputation will have been performed with subsequent tailoring of a prosthesis in mind. Relatively little proximal soft tissue debridement seems to have been required in many of the cases, with the exception of limbs with significant fragmentary contamination.

Associated injuries in this series were very variable, ranging from none to multiple system trauma. Only two of the reported casualties died after reaching medical care The low incidence of primary blast injury is to be expected and it is important to stress that the incidence of secondary missile injury would have been greatly reduced had the casualties been wearing contemporary body armour.

This study gives some guidance to the possible mechanism of traumatic amputation by explosive blast. The widely held view that dynamic overpressure is responsible for the traumatic avulsion of limbs has never been challenged. Furthermore, there is no reported evidence that primary or secondary fragments are capable of causing such severe disruption of a limb that amputation is inevitable. It might be expected that the effect of dynamic overpressure on the limb would be to cause flailing relative to the torso, leading ultimately to failure at the limit of movement of a joint. If this is the mechanism, traumatic amputation should show a high incidence of associated joint disruption, dislocation and fracture–dislocation

Study of the pattern of injury caused by wind blast in ejecting fast-jet pilots offers useful comparisons[10]. The pilot emerging from the aircraft cockpit is almost instantaneously exposed to the wind-blast effect of the high-velocity slipstream (400–700 knots (600–1100 km/h)). This causes flailing of the limbs, characteristically with rapid abduction and external rotation. The recorded injuries sustained in this way are predominantly sited around joints and there is a high incidence of ligament disruption and fracture–dislocation. There is an almost equal incidence of long-bone fracture, especially of the more proximal parts of the limbs. Traumatic amputation does not occur, despite wind velocities similar to those of the blast winds (dynamic overpressure) created by sizeable explosive charges.

The pattern of injury caused by aerodynamic wind blast seems to differ from that described in this series due to explosive blast, despite apparently similar dynamic forces acting on the limb. This suggests that the mechanisms of injury are dissimilar. The component of explosive blast that is not implicated in the forces acting on ejecting pilots is the shockwave with its sharp leading edge, the shock front It is now accepted that this shockwave and its associated stress waves within the chest are responsible for the tissue disruption that results in primary blast lung[11], rather than gross compression of the chest by the dynamic overpressure. It may also be possible that the shockwave is capable of disrupting soft tissue and bone in a limb, to the extent that traumatic amputation by the dynamic overpressure is facilitated, if not inevitable Preliminary experiments on bone aimed at delineating shock and dynamic overpressure effects have shown that the shockwave is capable of causing bone disruption. This work suggests that there is more to the mechanism of traumatic amputation due to blast than simple avulsion by the dynamic overpressure.

Further study of the pattern of injury in traumatic amputation caused by blast is required Because the majority of victims of such injury are killed by associated trauma, it seems most sensible to study forensic details of those who do not survive. It is also likely that assessment of the precise level of amputation and the degree of soft tissue damage incurred will be more accurately recorded, and that photography will be used, by those responsible for autopsy investigation Knowledge of the pattern of injury may allow the mechanism of injury to be understood. Only then can sensible and appropriate protection be developed for those involved in security duties

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Management of Gulf War casualties

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During the Gulf War 84 patients underwent surgery in the Jubail Armed Forces Hospital, Saudi Arabia. The median time to evacuate casualties to hospital was 8 h 40 min. Fragments caused 88 per cent of injuries; 11 per cent were caused by bullets. Multiple lesions were encountered in 70 per cent of patients. The extremities (76 per cent) were the most frequently injured site, the lower limbs more so than the upper. Soft tissue injuries prevailed (59 per cent).

During the Gulf War, Jubail was a key point for medical support of the allied forces. Field hospitals from Sweden, Norway, and the UK and two fleet hospitals from the USA were operating in the area. The Jubail Armed Forces Hospital has 100 beds and is situated in King Abdulaziz Naval Base, 200 km from the front. It received most of the casualties from the Arab allies' east wing.

The Gulf War had the following characteristics:

1. Complete allied air superiority, allowing safe and effective use of helicopters for evacuation.
2. A good road network, allowing expeditious and safe ground evacuation after injury
3. A good communications network, allowing advance knowledge of casualties.
4. Limited offensive actions, making conditions for the medical teams optimal.
5. Defensive types of weapons such as mines were responsible for the majority of casualties.
6. Unrealized expectations of high casualties, meaning that medical facilities were left with high reserves.

The management of casualties admitted to Jubail during the War is presented.

Patients and methods

A total of 157 war casualties were admitted between 15 January and 8 March 1991. Five patients had burns that were managed without operation. Some had wounds managed primarily in frontline field hospitals This surgery consisted mainly of amputation, abdominal exploration in unstable patients, and debridement for soft tissue injuries.

This paper reports details of the 84 patients undergoing surgery in Jubail Hospital. The receiving doctors followed a standard protocol that included the administration of pethidine, antibiotics and tetanus toxoid, ensuring an adequate intravenous line, determination of haematological and biochemical profiles, and obtaining blood group. Triage was carried out by the most senior surgeon, radiography was requested as needed.

For each patient the following details were recorded: name, hospital number, age, sex, nationality, vital data on admission, initial blood profile, time and mode of injury, scene of accident, preliminary supportive care, and anatomical site(s) and structure(s) injured. If multiple wounds were found in, for example, the upper limb, they were counted as one upper-limb injury Multiple wounds were frequently encountered but only those needing debridement under anaesthesia were counted The operative and postoperative course, period of hospital stay, and discharge to unit, home or to other medical facilities were recorded.

Results

The 84 casualties were mainly Saudi (69 patients), with one American and 14 from other Arab allies. Their median age was 23 (range 18–43) years.

There were 33 injuries (28 per cent) to the upper extremities, 55 (47 per cent) to the lower extremities, ten (9 per cent) to the head and neck, seven (6 per cent) to the abdomen and back, nine (8 per cent) to the chest and two (2 per cent) to the external genitalia. Multiple injuries occurred in 59 patients (70 per cent). Penetrating wounds were encountered in the abdomen in two patients, in the chest in two and in the head in two. Fragments caused injury in 74 patients (88 per cent), bullets in nine (11 per cent) and both in one.

The structures injured are shown in *Table 1*. The type of operation performed (150 procedures in 107 sessions on 84 patients) is shown in *Table 2*.

The time of injury was clearly established in 62 of the 84

Table 1 *Structures injured in 84 casualties receiving surgical treatment*

	No.
Soft tissue	79 (59)
Bones	28 (21)
Tendons	4 (3)
Vascular system	1 (1)
Kidneys	1 (1)
Urethra	1 (1)
Penis and scrotum	2 (1)
Lungs	1 (1)
Chest wall	4 (3)
Diaphragm	1 (1)
Stomach	1 (1)
Face (fractures)	1 (1)
Brain	2 (1)
Spinal cord	1 (1)
Eyes	7 (5)
Total	134 (100)

Values in parentheses are percentages

Table 2 *Procedures performed on 84 patients receiving surgical treatment*

	No.
Debridement for soft tissue injury	76 (51)
Extraction of foreign bodies	16 (11)
External fixation for fractures	11 (7)
Fasciotomy	2 (1)
Vascular repair (patching)	1 (1)
Tendon repair	3 (2)
Abdominal exploration	2 (1)
Thoracotomy	1 (1)
Corneoscleral repair	3 (2)
Enucleation of eye	1 (1)
Delayed primary suture	20 (13)
Minor amputation (foot, toes, etc)	6 (4)
Major amputation (below-knee, above-knee)	6 (4)
Urethral repair	1 (1)
Colostomy for diversion	1 (1)
Total	150 (100)

Values in parentheses are percentages

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casualties. The median delay between injury and the time the patient reached definitive surgical treatment was 8 h 40 min (range 1–25 h). Before the allied invasion of Kuwait, this time was 4 h 10 min (range 2–25 h) and afterwards 12 h 30 min (range 1–25 h).

The median hospital stay was 4 (range 1–16) days. Patients were evacuated further from the front for continued postoperative care (70 patients; 83 per cent), or discharged home or to unit (12 patients, 14 per cent). Two patients with penetrating head injuries needed immediate evacuation to a neurosurgical facility for specialized care. The diagnosis in these was made by computed tomography because the sites of the fragments in conventional radiographs did not coincide with the external wounds

Wound debridement was usually carried out by longitudinal extension of the wounds, exposing the underlying cavity, excising devitalized tissue, and cleaning the wound mechanically and by irrigation. Wounds were lightly packed and left open for delayed primary closure 3–5 days later[1] Complete fasciotomy for one or more leg compartments was needed in two patients

Injured hand tendons were repaired primarily after adequate debridement in three patients. The wounds were not markedly devitalized.

One injury to the posterior tibial artery caused by a fragment necessitated patch graft using saphenous vein after adequate debridement.

Nephrectomy was carried out in one patient with a penetrating bullet injury that shattered the parenchyma completely. This patient also had a comminuted fracture of the first lumbar vertebra with resultant paraplegia. A urethral injury was repaired primarily in a patient with an extensive pelvic wound involving the left buttock. A transverse colostomy was required for faecal diversion from the pelvic wound. Penile and scrotal wounds were adequately debrided and closed primarily with scrotal drainage These wounds healed primarily

Lung tears were found in one patient with chest wall trauma after a blast injury The same patient had a facial fracture that needed interdental occlusion. One diaphragmatic injury was caused by a fragment that penetrated the stomach. The stomach wounds were debrided and closed in two layers; the diaphragm was closed in two layers with non-absorbable sutures.

Seven patients had different types of injuries to the eyes; three corneoscleral repairs were carried out and one eye was enucleated.

There was no immediate mortality or morbidity, but long-term results were not available because of evacuation of the casualties and difficulties in tracing them.

Discussion

Field hospitals became particularly active after the start of the ground attack when the front moved forward dramatically and evacuation through the ground route became more time consuming The nature of wounds treated in the field hospitals was similar to those in this study[2].

Most patients were fit young adults and the majority were haemodynamically stable. Most had soft tissue injuries with varying degrees of contamination. The anatomical distribution of injuries in this study showed higher than expected numbers in the extremities. Previous sites of war wounds have been reported as: head and neck, 12 per cent, thorax, 16 per cent; abdomen, 11 per cent; and extremities, 61 per cent[3,4] In contrast, extremity wounds represented 76 per cent of injuries in the present study. This difference may be explained by the use of armoured vests by some allied troops or because of limited offensives by the enemy. Many injuries were caused by defensive mines, which inflicted more wounds to the extremities with lower mortality in those who survived to reach surgical facilities[5].

Most patients (70 per cent) had multiple lesions caused by fragments. Extraction of foreign bodies was carried out if a fragment was found during debridement. Additional wounds were not made. A limited number of foreign bodies were therefore extracted (16 procedures) in comparison with the 76 debridements for soft tissue injuries.

The number of operative sessions was 107, in which 150 procedures were performed, a mean of 1·3 sessions per patient. Delayed primary wound closure was carried out between days 3 and 5, and accounted for most additional surgery

When the front was 200 km from the hospital and before the ground war started, the median lag period was 4 h 10 min (e g. casualties from the battle for Khafji) After 24 February, when the ground attack started, the median delay was 12 h 30 min No difference in morbidity was noticed between these two periods, because of selection by frontline medical officers.

Fixed-base hospital facilities are valuable in the management of war casualties and patients fare better than in the mobile smaller field hospitals The only drawback is the time needed for evacuating the injured. Appropriate triage of casualties in frontline medical units and proper deployment of transportation and communication facilities allow the optimal use of the resources available

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Subcutaneous mastectomy with immediate reconstruction as treatment for early breast cancer

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Subcutaneous mastectomy and axillary dissection combined with immediate reconstruction was used to treat primary breast cancer in a consecutive series of 111 patients. Local recurrence occurred in 19 patients (17 per cent) during a mean follow-up of 30 (range 6–60) months. Complete control of local disease was achieved in all patients except one, who had terminal disease. Prophylactic radiotherapy was avoided for 83 per cent of patients, and good cosmetic results were obtained in 89 per cent. These results support the use of this technique in the treatment of early breast cancer.

With the increasing incidence of early detection of carcinoma of the breast, partly caused by a heightened public awareness and partly by screening, the debate about optimal local treatment continues. In terms of overall survival, lumpectomy provides good results for stage I and II breast cancer[1]. There has been concern about the long-term effectiveness of adjuvant radiotherapy in preventing local recurrence[2,3]. Cosmetic results, particularly for patients with medial tumours and small breasts, can be poor. Occasionally there is considerable morbidity from radiotherapy that is difficult to treat[4]. New techniques of subcutaneous mastectomy with immediate reconstruction using silicone implants have improved the cosmetic results Such results are generally good and a total clearance of breast tissue and adjacent axillary nodes can be achieved. There is no contraindication to subsequent radiotherapy.

Patients and methods

A consecutive series of 111 patients treated for breast cancer with subcutaneous mastectomy and immediate reconstruction between 1986 and 1990 was studied. Patient data were collected prospectively and confirmed by review of records at the time of census Details recorded included operative procedure, histological and pathological tumour variables, adjuvant therapy and disease recurrence.

Tumours were staged according to the tumour node metastasis (TNM) classification, with tumour size measured by the pathologist The survival data presented are the results of life-table analyses[5].

Indications

Subcutaneous mastectomy can be used in patients with diffuse *in situ* carcinoma and in those with invasive carcinoma who wish to avoid mastectomy or lumpectomy with radiotherapy Needle biopsy and mammography are performed before surgery to enable informed discussion of treatment options

Operative technique

Initially the implants were placed subpectorally in patients with little or no ptosis, but the problems of wound inflammation and rejection of the prosthesis have been overcome and nearly all prostheses are now placed subcutaneously, because of the improved cosmetic result with matching breasts The most satisfactory incision is usually horizontal from the lateral side of the nipple If the tumour is difficult to approach because of its medial position, then another horizontal incision is made medial to the nipple. The plane between the breast tissue and fat is opened by blunt dissection. Light skin tethering does not necessitate excision of skin if the tumour is some distance away The subareolar ducts are divided as they enter the nipple and no nipple-everting sutures are necessary If the nodes are not clinically involved, then the lower two-thirds of the axilla are cleared; with probable lymphatic involvement axillary dissection is performed Care must be taken when retracting the breast skin because excessive pressure can cause fat necrosis and subsequent prolonged erythema of the overlying skin Two suction drains are left in place.

The wound is irrigated with dilute povidone–iodine (Betadine, Napp Pharmaceuticals, Cambridge, UK) in normal saline (1.4) to dislodge any free fat, lobules of which are sucked off the surface of the irrigation fluid. The volume of the removed breast is measured by water displacement A trial prosthesis is placed in the pocket and the appearance compared with that of the opposite breast. All prostheses, from 75 ml to 500 ml, are low-bleed low-profile type; rough textured prostheses have recently been used[6] The skin is closed in two layers, with 4/0 PDS (Ethicon, Edinburgh, UK) to the fibrous subcuticular layer and 3/0 monofilament nylon sutures to the skin Adhesive paper tapes are applied between skin sutures A lateral pressure dressing is used for 48 h to keep the prosthesis in a medial position

The drains are removed when they have collected less than 10 ml on 2 consecutive days, 4 weeks is the longest that a drain has remained. Prophylactic antibiotics are administered with induction of anaesthesia and continued until the drains are removed. Patients are encouraged not to wear a brassière for 3 months

Capsulotomy

Capsule formation was measured by a modified Baker's classification (*Table 1*)[6] Significant capsules are readily treated by open capsulotomy, a delay of 9 months after initial operation is advised to allow maximal capsular contraction. At operation the prosthesis is removed and the capsule divided with scissors around the edge, separating the base of the pocket from the dome. A small suction drain is used Leaving the original contracted capsule in place limits the degree of further contraction, giving good long-term results

Results

Complete data were obtained for each of the 111 patients, who ranged in age from 26 to 76 (mean 51·7) years. Follow-up ranged from 6 to 60 (mean 30) months. Clinical and pathological data are shown in *Table 2*. In all cases histological examination confirmed that the resection margin was free from tumour. Recurrence data are shown in *Figure 1* and *Table 3*. Of 19 patients with local recurrence, 11 are alive and well with no residual disease, five have died from distant metastases, and three are alive but have been treated for distant or regional recurrence. When local recurrence developed, 12 patients underwent local excision and radiotherapy with local control, two underwent conversion to mastectomy followed by

Table 1 *Classification of capsule formation (modified after Baker)*

Grade	Description
1A	Ideal
1B	Edges and implant palpable, no complaints or distortion
2	Satisfactory (capsule obvious but not firm, no complaints or distortion)
3	Inferior (capsule firm; minimal distortion, uncomfortable)
4	Poor (firm to hard, look and feel abnormal; painful)

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Table 2 *Clinical and pathological features of breast cancer in 111 patients*

Variable	No. of patients
Skin tethering	
None	68 (61)
Mild	31 (28)
Marked	12 (11)
Tumour size (cm)	
<2	53 (48)
2–5	52 (47)
>5	6 (5)
Histology	
Ductal carcinoma *in situ*	13 (12)
Invasive ductal carcinoma	90 (81)
Lobular carcinoma	7 (6)
Other	1 (1)
Differentiation	
Good	16 (14)
Moderate	17 (15)
Poor	78 (70)
Lymph node status	
Positive	32 (29)
Negative	79 (71)

Values in parentheses are percentages

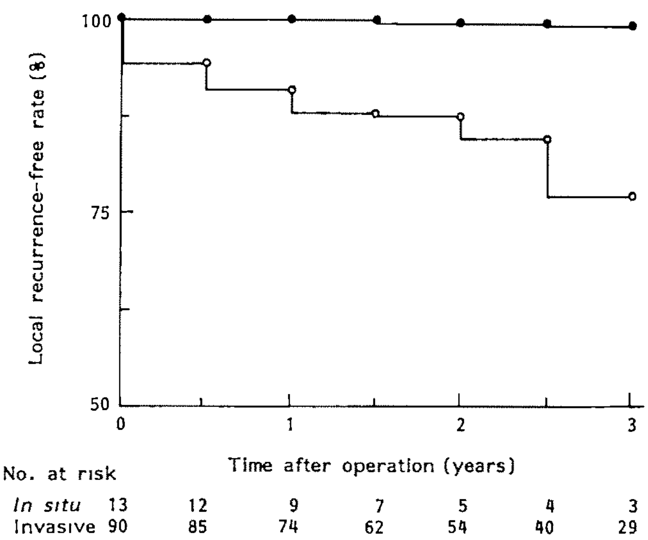

Figure 1 *Life-table analysis showing rate of local recurrence in 103 patients with ductal carcinoma according to tumour invasion* ●, *Ductal carcinoma* in situ, o, *invasive ductal carcinoma*

Table 3 *Recurrence rates and outcome in 111 patients with breast carcinoma*

	No. of patients	
	First event	All events
First recurrence		
Local	17 (15)	19 (17)
Regional	6 (5)	11 (10)
Distant	14 (13)	24 (22)
Combination of sites	2 (2)	39 (35)
Death from breast cancer	13 (12)	
Death from another cause	2 (2)	
Alive and free from local disease	95 (86)	

Values in parentheses are percentages

radiotherapy, three had wide resection of the breast skin flaps and reconstruction using latissimus dorsi flaps, and one had simple excision of a local recurrence but died shortly afterwards from distant disease. One patient presented for review with local recurrence and brain metastases that failed to respond to chemotherapy and died without further local surgery. Of the 19 patients, 18 had local control of disease. Of the 103 patients with ductal carcinoma, 31 had histologically proven axillary lymph node involvement. Of these, ten developed locoregional recurrence during follow-up. Larger tumours, even those that had been completely excised, were more prone to local recurrence (*Figure 2*).

The incidence and degree of capsule formation is shown in *Figure 3*. All developed within 1 year of initial surgery. Capsulotomy was performed in 13 patients (12 per cent). Of the 47 patients with a subcutaneous implant, nine developed severe capsule formation (modified Baker's grade 3 and 4). When the implant was placed subpectorally, severe capsule formation was observed in seven of 64 patients (11 per cent). Ideal or satisfactory cosmesis without a brassière has been

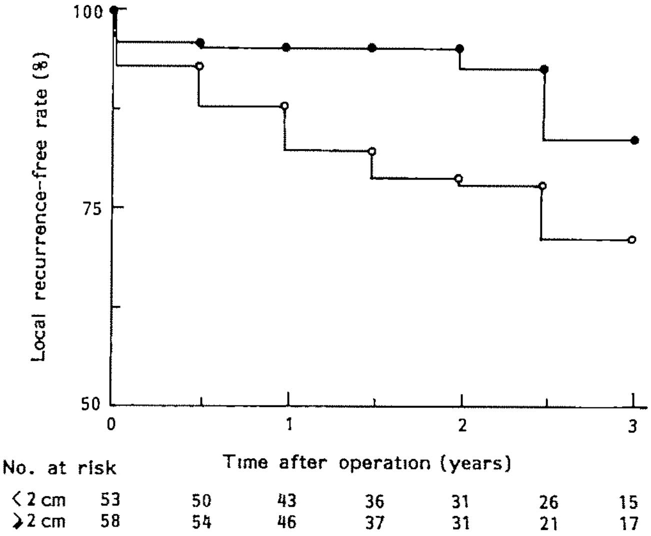

Figure 2 *Life-table analysis showing rate of local recurrence in 111 patients according to tumour size* ●, *<2 cm*, o, *≥2 cm*

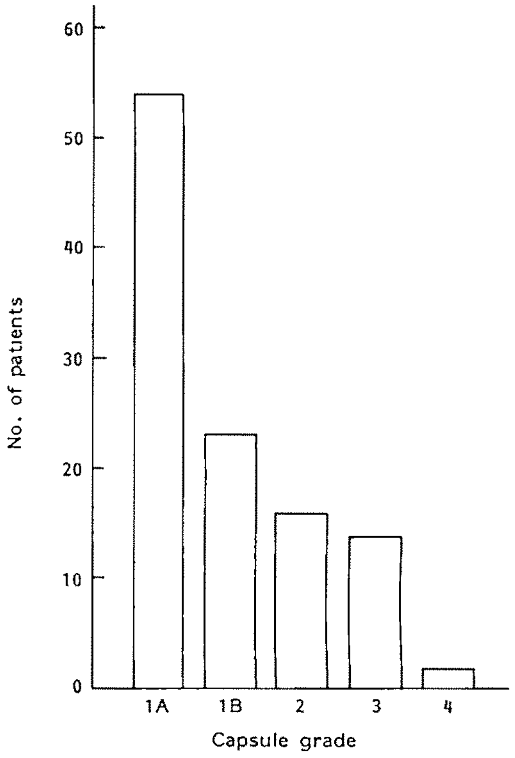

Figure 3 *Frequency and current degree of capsule formation in 109 patients (including those who have undergone capsulotomy) using the modified Baker classification described in* Table 1

achieved in 99 patients (89 per cent), including several with large pendulous breasts. Of the ten patients with inferior or poor results, four have declined capsulotomy and four await the procedure.

Discussion

Subcutaneous mastectomy has an established role in the management of benign breast disease that is refractory to medical therapy[7,8]. The operation has not been shown to be inferior to total mastectomy in terms of prognosis when performed prophylactically in those at risk[9]. Subcutaneous mastectomy has been advocated in the treatment of primary breast cancer. Reynier *et al.* reported a series of 106 patients undergoing subcutaneous mastectomy and radiotherapy, six of whom developed local recurrence; 70 per cent of patients were thought to have had a satisfactory cosmetic result[10]. A skin flap recurrence rate of 9 per cent was reported by Ward and Edwards using the method in 44 patients with breast cancer[11] The Nottingham group offered subcutaneous mastectomy to patients with breast cancer without skin involvement or deep fixation[12]; rates of local recurrence and survival were similar to those of simple mastectomy. A local recurrence rate in the present series of 17 per cent at a mean follow-up of 30 months may seem high, but for node-negative tumours <2 cm in size only four of 44 (9 per cent) had local recurrence. This is comparable to the rate observed by Fisher *et al.* for patients treated by wide local excision alone[1].

There are two major arguments against using subcutaneous mastectomy for breast cancer. The first is that the procedure gives inadequate clearance of breast tissue under the flaps and in the nipple. Skin preservation, however, does not cause additional risks of recurrence in patients with T_1 and T_2 tumours[13]. Occult carcinoma could remain in the nipple, although recurrent or new cancer in the preserved nipple appears to be rare[14–18]. Rosen and Tench studied 101 mastectomy specimens from patients with breast cancer[19]; breast lobules were found in 17 nipples and carcinoma in 13, although the tumours were largely non-invasive. They concluded that nipple involvement was associated with axillary lymph node metastases, centrally placed tumours, tumour size >2 cm and lymphatic tumour emboli observed in the mastectomy specimen. A much larger study indicated that nipple involvement was associated with macroscopic nipple abnormality in nearly 90 per cent of cases[20].

The second argument against subcutaneous mastectomy relates to the complications of the procedure. Capsular contraction requiring surgery may occur in up to 10 per cent of cases, although it may occur in 74 per cent after long-term follow-up[21,22]. Other reported complications include infection, haematoma formation, implant extrusion, nipple or areolar necrosis, skin flap necrosis and, more recently, toxic shock syndrome[21,23–27]. The use of the plane between the deep fat and breast tissue has enabled thick flaps to be used, giving good cosmesis. Capsular contraction is readily corrected by open capsulotomy with excellent results and no complications.

The policy of deferring radiotherapy until first recurrence has meant that 83 per cent of patients avoided this treatment. Local recurrence has been easily treated by local excision and, usually, radiotherapy

The operation of subcutaneous mastectomy, with its good cosmetic results, may reduce the psychological trauma associated with deforming breast surgery[28–30].

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Regional variation in the surgical treatment of early breast cancer

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A questionnaire survey of consultant surgeons in England was undertaken to establish the preferred surgical management of early breast cancer. The Regional Health Authority in which each surgeon worked was recorded to document regional variation. The 14 Regional Health Authorities were divided into three geographical areas: north, central and south. The main finding was that proportionately more surgeons in the north would recommend mastectomy ($P < 0{\cdot}0001$) *rather than conservative surgery compared with those in the central and southern areas. The nature of the study does not allow explanations for such variation.*

The results from a follow-up questionnaire survey demonstrated significant changes in the surgical management of patients with $T_{1/2} N_0 M_0$ tumours of the breast since publication of an earlier survey undertaken by the same authors[1]. The findings were: (1) a significant increase in the number of surgeons who would undertake conservative surgery; (2) a significant rise in the number who would discuss breast reconstruction when mastectomy was the preferred treatment; (3) significantly more surgeons would offer the patient a choice of surgery if there was more than one option; and (4) significantly more surgeons had access to a breast specialist nurse and/or cancer counsellor[2].

Recent comment in the media[3] has highlighted that the treatment for cancer varies according to where patients are treated, but little work has been undertaken with respect to breast cancer surgery. Two studies in the USA have indicated that there is geographical variation in the treatment of breast cancer[4,5].

The follow-up questionnaire survey undertaken by Morris *et al.*[2] focused on the surgical management of breast cancer in England as a whole. Information was collected, however, about the Regional Health Authority (RHA) in which each surgeon operated and it was thus possible to determine whether there were differences between surgeons in different RHAs.

Methods

To establish the extent to which surgical practice had altered, the first part of the follow-up questionnaire contained the same questions as the original survey. These established: the numbers of newly diagnosed patients with breast cancer treated in 1989 and 1990, the preferred surgery for a 40-year-old woman with a $T_{1/2} N_0 M_0$ tumour in the upper outer breast quadrant, the extent to which patients were offered a choice of surgery, the extent to which written information was provided, factors that influenced choice of treatment, availability of breast reconstruction; availability of breast specialist nurses, amount of time spent with patients in the outpatient clinic.

The second part of the questionnaire was designed to quantify the preferred treatment for ductal carcinoma *in situ*, these results will be reported separately.

By writing to each RHA a list was obtained of the names and addresses of 873 consultant surgeons in England. The numbers in each RHA were: Northern, 70, Yorkshire, 75, Trent, 60; East Anglia, 29, North-west Thames, 66, North-east Thames, 85, South-east Thames, 48, South-west Thames, 47, Wessex, 46, Oxford, 48, South-western, 64, West Midlands, 129, Mersey, 40, and North-western, 66.

The questionnaires were posted to consultants during the period May to October 1991.

Results

Data were analysed using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA) on a VAX cluster running the VMS operating system.

Response to questionnaire

Of the 873 consultants approached, a total of 468 responses were received by the end of December 1991, a response rate of 53·6 per cent. These comprised 443 questionnaires (all or some questions answered), eight letters and 17 unanswered questionnaires. Stated reasons for non-completion were: surgeon retired ($n = 14$), surgeon died ($n = 1$), no time to complete the questionnaire ($n = 2$), surgeon on sabbatical leave ($n = 1$), and surgeon not treating patients with breast cancer ($n = 2$).

The results of the survey are based on responses from 358 surgeons (80·8 per cent of those who completed the questionnaire) who indicated that they currently treated patients with breast disease. Any discrepancy between the response to each question and the overall sample of 358 is due to missing data.

Number of patients with breast cancer treated

In 1989, the median number of patients treated was 25 (range 0–631). In 1990, the median was 30 (range 0–718). This compares with a median of 25 (range 3–321) in 1985.

Response rate by Regional Health Authority

Of the 358 consultants who reported that they treated patients with breast disease, 334 indicated the RHA in which they worked: Northern, 16, Yorkshire, 30; Trent, 37; East Anglia, 15, North-west Thames, 19, North-east Thames, 23; South-east Thames, 22; South-west Thames, 15; Wessex, 22; Oxford, 16; South-western, 30; West Midlands, 53, Mersey, 12; and North-western, 24.

The response rate by region and data on the median number of patients treated in 1990 are shown in *Table 1*. To examine whether there were geographical differences in surgical practice, the regions were grouped into three areas to increase the size of the sample (examination of the *Health Service Journal* map of the National Health Service gave rise to these areas) (*Table 2*). The three areas were: north ($n = 70$ – Northern, Yorkshire and North-western RHAs); central ($n = 102$ – Trent, West Midlands and Mersey RHAs); and south ($n = 162$ – East Anglia, the four Thames RHAs, Wessex, Oxford and South-western RHAs).

There were no significant differences between these three areas regarding numbers of patients with breast cancer treated in 1990, the extent to which surgeons would offer the patient a choice of treatment, whether or not reconstruction would be discussed when mastectomy was the preferred form of treatment, and whether or not the surgeons had access to a breast specialist nurse or cancer counsellor.

There was a significant difference, however, in the type of treatment surgeons would recommend. For a $T_{1/2} N_0 M_0$

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Table 1 *Questionnaires received from each Regional Health Authority*

Regional Health Authority	Questionnaires posted	Questionnaires received	No. of surgeons responding who treated breast disease	Median no. of patients with breast disease treated in 1990
Northern	70	23 (33)	16 (70)	22·5
Yorkshire	75	39 (52)	30 (77)	32·5
Trent	60	46 (77)	37 (80)	25
East Anglia	29	17 (59)	15 (88)	40
North-west Thames	66	27 (41)	19 (70)	20
North-east Thames	85	33 (39)	23 (70)	20
South-east Thames	48	25 (52)	22 (88)	51
South-west Thames	47	18 (38)	15 (83)	20
Wessex	46	28 (61)	22 (79)	45
Oxford	48	22 (46)	16 (73)	18·5
South-western	64	36 (56)	30 (83)	40
West Midlands	129	57 (44)	53 (93)	30
Mersey	40	15 (38)	12 (80)	25
North-western	66	32 (48)	24 (75)	20

Values in parentheses are percentages

Table 2 *Surgical treatment recommended for a $T_{1/2} N_0 M_0$ tumour located in the upper outer breast quadrant of a 40-year-old woman*

	No of surgeons who would undertake	
Regional Health Authority	Mastectomy	Wide excision
North		
Northern	1 (9)	10 (91)
Yorkshire	5 (19)	21 (81)
North-western	8 (40)	12 (60)
Total	14 (25)	43 (75)
Central		
Trent	3 (11)	25 (89)
West Midlands	1 (2)	47 (98)
Mersey	2 (15)	11 (85)
Total	6 (7)	83 (93)
South		
East Anglia	0 (0)	15 (100)
North-west Thames	2 (11)	17 (89)
North-east Thames	1 (4)	22 (96)
South-east Thames	2 (10)	18 (90)
South-west Thames	1 (6)	15 (94)
Wessex	0 (0)	22 (100)
Oxford	0 (0)	14 (100)
South-western	1 (3)	30 (97)
Total	7 (4)	153 (96)
Overall total	27 (9)	279 (91)

Values in parentheses are percentages

tumour located in the upper outer breast quadrant of a 40-year-old woman, proportionately more surgeons in the north would recommend mastectomy (52 per cent) compared with those in the central (22 per cent) and southern (26 per cent) areas ($\chi^2 = 21{\cdot}96$, 2 d.f., $P < 0{\cdot}0001$). This difference was largely accounted for by the preference for mastectomy of surgeons in the North-western RHA (40 per cent) rather than those in the Yorkshire (19 per cent) or Northern (9 per cent) RHAs (*Table 2*).

Discussion

The relatively small number of surgeons from each RHA who participated in this survey prohibits any firm conclusions being drawn.

The implications of the results are best considered in the context of quality assurance and the setting of contracts for certain types of treatment. While there are no published data on the relative costs and consequences (e.g. clinical efficacy and quality of life) of mastectomy and breast-conserving surgery in England, prices have to be established and standards of care set for treatment alternatives to assist in contract setting

Why should a relatively large proportion of surgeons in the North-western RHA choose mastectomy as treatment for a $T_{1/2} N_0 M_0$ tumour? Is such variation a reflection of the attitude of the surgeons concerned, as suggested by Liberati *et al.*[6] in a study of Italian doctors? This paper may stimulate discussion and/or encourage further research.

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Tumour oestrogen receptor content allows selection of elderly patients with breast cancer for conservative tamoxifen treatment

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Immunocytochemical analysis was used to determine tumour oestrogen receptor (ER) content in elderly patients with primary operable breast cancer. Only those ER positive were selected for conservative treatment with tamoxifen alone. Initial response was compared with that of historical controls not selected according to ER status. Early progressive disease was markedly reduced at 6 months, from 30 per cent in the unselected control group to 2 per cent in the study group ($P < 0.001$). *Immunocytochemical analysis is useful for the initial selection of elderly patients with breast cancer who may be treated with tamoxifen alone.*

Tamoxifen can be used as an alternative to surgery for the treatment of primary operable breast cancer in the elderly[1–4]. Two randomized prospective trials comparing surgery with tamoxifen have shown no difference in overall survival in the two treatment groups[5,6]. The latter trial[6] examined only tumours <5 cm in diameter. Although there was no difference in survival between the two groups, surgery gave significantly better ultimate control of primary disease than did tamoxifen treatment, largely because of a high rate (30 per cent) of initial disease progression on tamoxifen. Disease in a further 14 per cent of patients progressed after an initially favourable response. Mastectomy should therefore be considered the optimal initial approach. However, in one-third of patients long-term local control was achieved with tamoxifen for up to 5 years, suggesting that this drug might benefit selected patients.

Oestrogen receptor immunocytochemical analysis (ER-ICA) of fine-needle aspirates of breast cancer is a good predictor of response to hormonal treatment[7–9]. In these studies, patients received the same treatment regardless of the ER-ICA result. In the present trial of surgery *versus* tamoxifen, the ER-ICA result has been used to select elderly patients with primary operable breast cancer for treatment with tamoxifen alone.

Patients and methods

Since February 1989, 139 patients over 70 years of age with primary operable breast cancer ($T_{1/2} N_{0/1} M_0$) and fit for surgery have been studied prospectively.

Fine-needle aspirates were obtained for diagnosis and ER measurement by ER-ICA. Specimens were smeared on to glass slides (three slides for ER-ICA: two for the assay, one in reserve) and air-dried.

Specimens for ER-ICA were fixed within 30 min of sampling in 10 per cent neutral buffered formalin for 10 min, followed by 100 per cent methanol at −10 to −20°C for 3 min, then acetone at −10 to −20°C for 2 min. Slides were then washed in Tris-buffered saline (pH 7·5–7·6) and kept in a buffered glycerol–sucrose storage medium at −20°C. ER-ICA was performed weekly using a kit (Abbott Laboratories, North Chicago, Illinois, USA) with monoclonal antibody H-222, and a subsequent staining procedure as has been previously described[10].

Quantification of ER-ICA results was performed by assessment of the intensity of nuclear staining (no staining, 0; staining weak but above background level, 1; moderate staining, 2; strong or intense staining, 3) and the percentage of cells at each level of intensity. A histochemical score (*H* score[11]) was derived from these two parameters:

$$\begin{aligned}\text{ER-ICA } H \text{ score} = {} & (\text{percentage of cells stained at intensity category 1})\\ & + 2 \times (\text{percentage of cells stained at intensity category 2})\\ & + 3 \times (\text{percentage of cells stained at intensity category 3})\end{aligned}$$

This formula produces an *H* score between 0 and 300, where 300 represents 100 per cent of tumour cells stained strongly. A minimum of 100 cells per sample was considered necessary for a satisfactory assay. Repeat fine-needle aspiration was carried out if specimens were inadequate.

For the purposes of the trial, *H* scores <100 were considered ER negative and those ≥100, positive. Patients who were ER positive were randomized to a trial of surgery *versus* tamoxifen alone (20 mg twice daily). All patients with ER-negative tumours were excluded from the trial and treated surgically.

Response to treatment with tamoxifen was assessed clinically by measuring tumour size at intervals of 3 months. Patients were assigned to one of four categories of response (progression, disease static, partial regression and complete regression) using Union Internacional Contra la Cancrum criteria[12]. Response was determined at 3 and 6 months, and on subsequent follow-up, unless there was earlier disease progression. The 'best assessment' of response to tamoxifen represents patients with disease that was static at 6 months, going on to partial or complete regression, and those with partial regression at 6 months going on to complete regression (i.e. it is the best response of each patient to date).

Tamoxifen treatment was continued as long as there was no evidence of progression, at which point mastectomy was recommended.

Results

To date, a total of 139 patients have been studied, of whom 23 (17 per cent) had inadequate specimens for ER-ICA requiring repeat fine-needle aspiration. ER-ICA scores were ≥100 in 98 patients, and these were randomized to a trial of surgery ($n = 44$) *versus* tamoxifen ($n = 54$). A total of 41 patients had ER-ICA scores <100 and were excluded from the trial. This report examines the group of 54 ER-positive patients treated with tamoxifen alone, of whom 50 could be assessed for initial response. The mean age in this group was 78 (range 70–87) years with a median follow-up of 13 (range 3–31) months. The median tumour size was 3 (range 1–5) cm.

Response to tamoxifen is shown in *Table 1*. Objective regression (partial or complete) was achieved in 43 patients on best assessment. Almost all of these showed at least partial regression at 6 months: only one patient (with an ER-ICA score of 200) showed initial progression of disease, at 3 months.

In *Table 2* these results are compared with those of historical controls: 57 patients from a previous trial[6] who were similarly treated and assessed but who were not selected with regard to ER status. At 6 months there is a marked reduction in the number of those with early progression, from 30 per cent in the unselected control group to 2 per cent in the present study group ($\chi^2 = 13{\cdot}8$, 1 d.f., $P < 0{\cdot}001$).

The distribution of individual ER-ICA scores in patients with a favourable initial response is shown in *Figure 1*. There

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Table 1 *Initial response to tamoxifen*

	Time of assessment		
	3 months	6 months	Best assessment
Complete regression	14	21	26
Partial regression	22	19	17
Disease static	13	6	6
Progression of disease	1	1	1
Total	50	47*	50

*In three patients follow-up was <6 months; at 3 months regression was partial in two patients and disease static in one

Table 2 *Comparison of present results with historical controls*

Response at 6 months	Oestrogen receptor-positive group	Unselected control group*
Complete regression	21	22
Partial regression	19	9
Disease static	6	9
Progression of disease	1	17
Total	47	57

*From Robertson *et al.*[6]

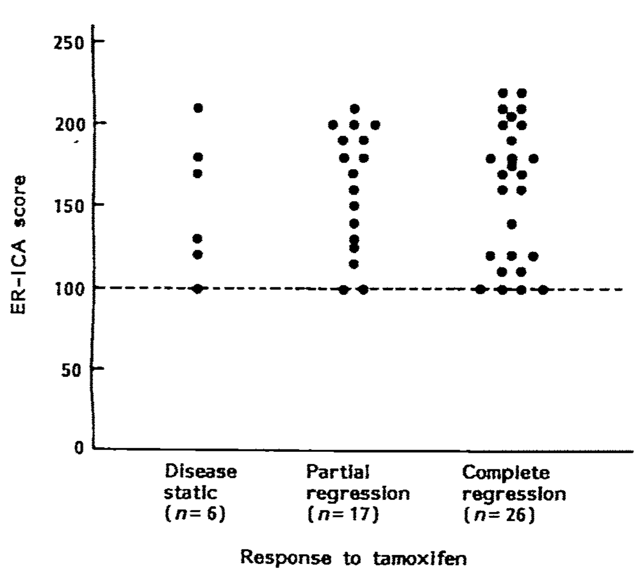
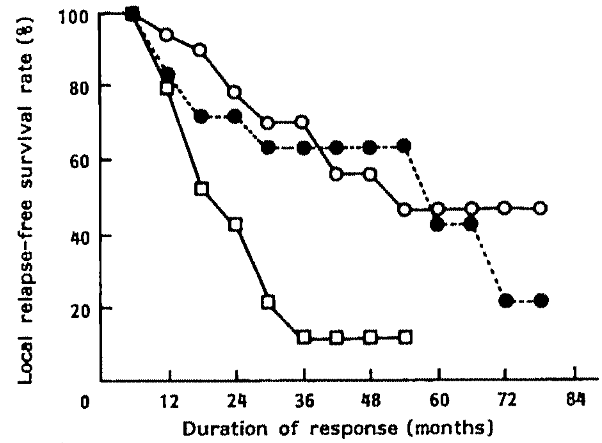


Figure 1 *Oestrogen receptor immunocytochemical analysis (ER-ICA) score according to type of response.* $r_s = 0.05$

Table 3 *Secondary progression of disease in five patients treated with tamoxifen alone*

Patient no.	ER-ICA score	Initial response	Duration of response (months)
1	120	Complete regression	22
2	100	Partial regression	15
3	190	Partial regression	11
4	130	Disease static	10
5	210	Disease static	9

ER-ICA, oestrogen receptor immunocytochemical analysis



No. at risk							
Complete	53	41	22	15	11	7	6
Partial	28	16	8	6	3	2	1
Static	16	9	4	1	1	–	–

Figure 2 *Duration of response according to type: complete regression* (○), *partial regression* (●), *and disease static* (□). *Patients with static disease have poorer local control than complete responders* ($\chi^2 = 8.9$, *1 d.f.*, $P < 0.01$) *and partial responders* ($\chi^2 = 4.2$, *1 d.f.*, $P < 0.05$) *by log rank test*

was a trend towards a larger proportion of high scores (>150) from static disease to complete regression.

To date, five patients with a favourable initial response have suffered local relapse (*Table 3*). *Figure 2* shows the actuarial local relapse-free survival rate according to the type of initial response (excluding initial progressors) in patients from past and present trials treated with tamoxifen alone. (The previous study[6] has been updated for best assessment of response[13] and these data then combined with those of the present study.)

Discussion

This randomized trial attempts to identify a group of elderly patients who will benefit from tamoxifen treatment alone and retests the hypothesis that some patients with operable breast cancer can be spared surgery. Tamoxifen does not compromise overall survival, but has questionable efficacy in controlling locoregional disease. The solution to this problem may lie in good patient selection, two aspects of which need to be addressed.

Initial response

A proportion (up to 35 per cent) of tumours will continue to progress in patients receiving tamoxifen. Gaskell *et al.*[8] found that it was possible to predict early progression of tumours (40 per cent locally advanced) using ER-ICA: when more than 25 per cent of cells were immunostained there was no incidence of early progression, but below this level 86 per cent of tumours progressed. Using the same cut-off value, Davies *et al.*[9] studied a similar group of patients and reported a 93 per cent rate of initial progression in those with ER-ICA-negative tumours against 9 per cent in those with ER-ICA-positive tumours. The present study confirms the effectiveness of ER-ICA in selecting out the patients likely to have early progression from those likely to have a favourable initial response to tamoxifen.

Duration of response

Patients with a favourable initial response to tamoxifen show a definite risk of subsequent local relapse. Horobin *et al.*[4] followed 113 patients over 5 years with primary breast cancer treated with tamoxifen only and found that disease control eventually failed in 62 per cent. They observed that tamoxifen, in effect, only delayed more definitive therapy. While ER-ICA appears to be effective in selecting those whose disease will progress early, it is less useful in predicting the duration of response. Reports from Horobin *et al.*[4], Falk *et al.*[14], and the present data indicate that the duration of response may be related to the type of response.

It may be possible to select patients for long-term treatment with tamoxifen in two stages. ER-ICA should be used initially to select out those tumours likely to progress early and which should be treated with surgery. The remaining patients should be treated with tamoxifen and a second selection carried out at 6 months. Those with static disease are at high risk of local relapse and should be considered for surgery

Acknowledgements

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Indications for primary tamoxifen therapy in elderly women with breast cancer

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A group of 66 elderly women with primary breast cancer were treated with tamoxifen and followed for a minimum of 2 years. Of these, 32 whose disease remained controlled for the 2-year period were considered to have had a 'worthwhile' response, 27 in whom disease progressed were considered to have had an unsatisfactory result and seven opted for alternative treatment. By Union Internacional Contra la Cancrum (UICC) criteria, 14 women had a complete response, 20 a partial response, in five disease remained static and in 20 it progressed without response. Prediction of outcome after assessment according to UICC criteria at 3 and 6 months was unsatisfactory (19 and 34 of 59 correctly predicted respectively). Analysis of multiple tumour measurements over 12 weeks was no better (33 of 59 correctly predicted). Immunocytochemical assay of fine-needle aspirates for oestrogen receptor (ER) provided a better predictor (38 of 47 correct) and the difference in survival between patients with and without ER activity was significant ($P < 0{\cdot}001$). Conventional assessments of response at 3 and 6 months are unsatisfactory for judging the long-term benefit to the patient. ER status is the best predictor of response and outcome.

There has been increasing interest in treating clinically localized breast cancer in elderly women with tamoxifen. Between 40 and 60 per cent of women can expect regression of the primary tumour, complete in approximately 25 per cent with another 20 per cent achieving stabilization[1,2].

Reports of two controlled randomized trials comparing tamoxifen with surgical treatment initially indicated that survival is not compromised, even when a lack of response or a relapse demands subsequent local treatment[3,4]. Concern remains that relapse rates may be high and that delay in surgical treatment may introduce additional hazards for these elderly patients. This is supported by preliminary results of a third trial comparing tamoxifen alone with tamoxifen plus optimal surgery[5,6]. Not only did relapse (necessitating a change of management) occur more frequently in women receiving tamoxifen alone, but there was also a reduction in survival.

Assessment of the response of a primary tumour to tamoxifen can take many months; a good predictor of response would therefore be of value. This study examines three methods of predicting response to tamoxifen. These included standard Union Internacional Contra la Cancrum (UICC) criteria 3 and 6 months after the start of tamoxifen treatment[7], sequential measurements of tumour size during the first 3 months of treatment[8], and the immunocytochemical assay of oestrogen receptor (ER-ICA) on fine-needle aspirates from the tumour. Previously reported work shows that it is possible to define a subset of patients with few receptor-positive cells who are unlikely to respond to treatment[9–11].

Patients and methods

Sixty-nine patients aged ≥ 70 years with 'operable' primary breast cancer agreed to participate. Diagnosis was established by clinical examination, mammography and fine-needle aspiration cytology. Investigations for metastatic disease including chest, skull and pelvic radiographs, and biochemical and haematological tests were negative. For the ER-ICA, a portion of the fine-needle aspirate of the tumour was immediately suspended in tissue culture medium for further processing. All patients had expressed a preference for primary treatment with tamoxifen and had agreed to attend for regular measurements of tumour size during the first 12 weeks of treatment. Two patients died and one abandoned follow-up within a month, 66 remained, 48 of tumour node metastases[12] stages I and II, and 18 of stage III.

Before commencement of tamoxifen therapy, tumour dimensions were measured in four axes using calipers and the mean diameter calculated. Tamoxifen was commenced in a dose of 20 mg daily, in eight patients an initial single loading dose of 160 mg was used.

Follow-up

Depending on fitness and accessibility, patients attended at 2–4-week intervals during the initial 12 weeks of the study. At each attendance, measurements of tumour size in four axes were repeated by the same observer. Further follow-up was at 2-month intervals for 6 months and then 3-monthly for at least 2 years. At these visits, tumour size was measured in only two diameters according to UICC criteria[12].

Assessment of response

Successful control of the tumour by primary tamoxifen therapy is referred to as a 'worthwhile' response. This is maintenance of regression or stabilization of the tumour (as defined by UICC criteria) over a minimum period of 2 years. Patients with tumour regression or stabilization who died or became chronically ill from causes other than breast cancer during the 2-year period were classified as having a worthwhile response provided there was no relapse of disease. Seven patients, all with stable disease, who chose to have local surgery (six) or radiotherapy (one) at 18–33 weeks after starting treatment were excluded from response comparisons but included in life-table analyses. 'Failures' of treatment were defined as (1) those having an initial response by UICC criteria but who relapsed within the 2-year period and (2) those with progressive disease from the start, or after initially appearing static.

Predictors of response studied

Union Internacional Contra la Cancrum criteria. The product of the largest diameter and its 90° partner was used to determine response at 3 and 6 months. By UICC criteria, regression is at least 50 per cent reduction in this product[7]. Complete regression was recorded if there was no palpable mass remaining. The presence of a vague residual thickening in the region of the tumour did not preclude regression. Progression was an increase of over 25 per cent in tumour size or the development of other signs of advancing local or metastatic disease.

For completeness, the 'best' response in terms of UICC criteria, irrespective of time, was also recorded.

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Sequential measurements. A regression line was fitted by the method of least squares to the calculated means of the four measured diameters of the tumour during the first 12 weeks of therapy, as previously described[8,13]. It was intended that response should be classified as significant tumour regression, progression or stasis depending on the significance of the deviation of the slope from horizontal. During the 12-week period of observation the downward slope of the curve was significant in only 19 patients (termed a statistical response); those slopes, which statistically were classified as stasis, were further examined independently by four observers and divided into two groups: those that showed a steady and consistent trend of reduction in tumour size (subjective response) and those in which no clear change could be ascertained (true stasis).

Oestrogen receptor immunocytochemical assay. The method has been described in detail previously[14,15]. Three cytospin specimens were prepared. Two slides (control and test) were fixed in 3·7 per cent formaldehyde–phosphate-buffered saline followed by methanol and acetone at −20°C and stored in sucrose–glycerol buffer; the third slide was air-dried and Giemsa-stained to provide control cytology.

The assay was carried out within 2 weeks using the ER-ICA kit (Abbott Laboratories, Maidenhead, UK).

The proportion of cells stained for ER was assessed independently by two observers. A cut-off of 20 per cent of cells stained was used to define 'significant' receptor activity.

Results

Worthwhile response

Thirty-two patients had worthwhile control of the tumour (worthwhile response) that persisted for 2 years: 14 had complete regression, 13 partial regression and five persisting stasis. Twenty-seven patients had progressive disease by 2 years. Seven of these had achieved a partial response but subsequently relapsed at a mean of 51 (range 24–100) weeks while disease in the other 20 had steadily progressed (*Table 1*).

Potential predictors of response

The assessment of responses at 3 and 6 months are summarized in *Table 2* and their relationship to worthwhile response at 2 years in *Table 3*.

Union Internacional Contra la Cancrum criteria. The 3-month assessment of regression (complete and partial) by UICC criteria correctly predicted only seven of 32 patients who had a worthwhile response. Conversely, it predicted 12 of 27 patients who failed to achieve this. The value of UICC criteria of regression at 6 months in predicting worthwhile response and failure was better (16 of 32 and 18 of 27 respectively), but there was still a small group of patients who, despite a response, were subsequently to progress. The best response assessed by conventional UICC criteria during the 2-year period gave an incidence for complete regression of 24 per cent (14 patients), for partial regression 34 per cent (20) and for stasis 8 per cent (five) of the 59 patients assessed.

Sequential measurements of tumour diameter. By statistical analysis of multiple measurements, 19 patients showed tumour regression, 28 stasis and 12 progression. When the data for the 28 with stasis were further examined subjectively, ten showed a steady but non-significant reduction in tumour size, and disease in 18 patients was truly static by either subjective or statistical criteria.

Of the 19 patients with tumour regression by statistical criteria, 14 (74 per cent) went on to have a worthwhile response. Equally, seven of the ten in whom early measurement had

Table 1 *Assessment of the benefits of tamoxifen after 2 years in 66 elderly patients with breast cancer*

Outcome	No.	Total
Worthwhile response		
Complete regression	14	32 (48)
Partial regression	13	
Stasis	5	
Failure (long-term)		
Early relapse	7	27 (41)
Progression	20	
Opted out	7	7 (11)

Values in parentheses are percentages

Table 2 *Number of patients responding to tamoxifen by Union Internacional Contra la Cancrum criteria and sequential tumour measurements*

	Regression			
	Complete	Partial	Stasis	Progression
UICC				
3 months	1	11	35	12
6 months	5	16	20	18
Best	14	20	5	20
Sequential measurements				
Statistically significant	19		28	12
Total (including subjective assessment)	29		18	12

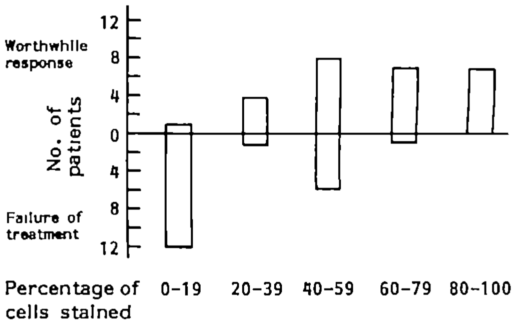

Figure 1 *Numbers of patients who achieved a worthwhile response and those who failed on 2 years of treatment with tamoxifen according to the percentages of cells positive by the oestrogen receptor immunocytochemical assay The seven patients who opted out are excluded*

Table 3 *Prediction of outcome of treatment at 2 years by the three different techniques*

Predictive technique	Total no. of patients	Predicted worthwhile response	Sensitivity (%)	Predicted treatment failure	Specificity (%)
UICC					
3 months	59	7 of 32	22	12 of 27	44
6 months	59	16 of 32	50	18 of 27	67
Sequential measurements	59	21 of 32	66	12 of 27	44
ER-ICA (< or ≥20% of cells stained)	47	26 of 27	96	12 of 20	60

UICC, Union Internacional Contra la Cancrum; ER-ICA, oestrogen receptor immunocytochemical assay

Table 4 *Relationship of percentage of cells stained on oestrogen receptor immunocytochemical assay to best recorded response in 47 patients*

Percentage of cells stained	Best response by UICC criteria			
	Regression			
	Complete	Partial	Stasis	Progression
0	0	0	0	6
1–19	0	2	1*	4
20–59	4	8	4*	3
60–100	8	7	0	0
Total	12	17	5*	13

UICC, Union Internacional Contra la Cancrum. *Two of the five went on to progress within 2 years

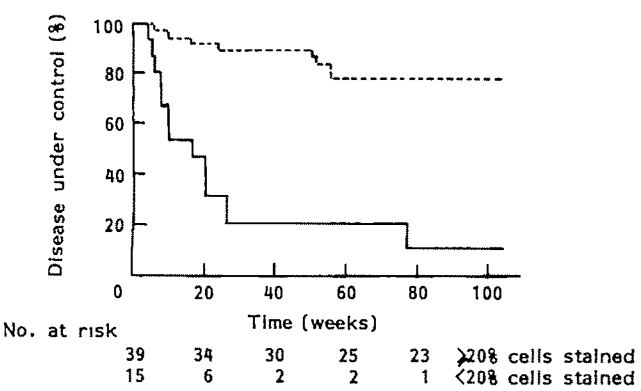

Figure 2 *Life-table analysis showing the probability of breast cancer remaining under control with tamoxifen for 54 women whose fine-needle aspirates were subjected to oestrogen receptor immunocytochemical assay* ($\chi^2 = 27 \cdot 37$, *1 d.f.*, $P < 0.001$). *The seven women who opted out at various stages during treatment are included.* ——, *<20 per cent of cells staining,* -----, *≥20 per cent of cells staining*

shown only subjective regression had a worthwhile response at 2 years. In contrast, all 12 of those tumours that either increased significantly in size (ten) or progressed locally (two) continued to progress over the study period.

Immunocytochemical assay. The relationships of the proportion of cells stained on ER-ICA to worthwhile and best responses are shown in *Tables 3* and *4* and *Figure 1*. All tumours reported to show no evidence of immunocytochemical staining progressed rapidly within 4 months. For those with receptor-positive cells present, there was a gradient of response between the proportion of cells stained and the incidence of response (*Table 4*). Life-table analysis for freedom from disease during the 2-year period according to ER status of the tumour is shown in *Figure 2*. The difference in survival between patients with ER-positive and ER-negative tumours is significant ($P < 0.001$).

Discussion

This study indicates that, over a minimum period of 2 years, primary tamoxifen therapy in women over 70 years of age gave a best response rate of 66 per cent that, when extrapolated to control of disease or until death and/or disability, was 54 per cent. In half of these patients, the tumour regressed completely.

This figure is lower than the best response rate of 78·7 per cent observed by Horobin *et al.*[1], who reported that in 30 per cent of patients control of disease was maintained for 5 years. In the present study no patient who achieved a complete response to tamoxifen therapy had disease progression within 2 years, a finding in agreement with the longer duration of responses reported by Horobin *et al.* for patients with complete compared with partial remission or static disease.

The rate of response to tamoxifen can be slow. In the present study the interval between the start of treatment and achieving UICC criteria for partial response varied from 4 to 88 (mean 21) weeks, and for complete response from 8 to 144 (mean 49) weeks, a finding similar to that reported by Horobin *et al.*[1]. An attempt was made to determine whether a prediction of response could be made at an early stage in treatment. Application of UICC criteria at fixed periods of time at 3 and 6 months did not allow this prediction in more than 50 per cent of patients (*Table 3*). This failure was due to the proportion of apparently static tumours that eventually progressed and others that initially showed a partial response but relapsed early. A proportion of those tumours that were apparently static after 6 months remained under control or regressed in the long term.

The analysis of multiple measurements of tumour size over the first 12 weeks of treatment was little better. Only a proportion of those in whom visual examination of the best-fit line showed a statistically significant reduction in tumour size went on to achieve a worthwhile response. Irrespective of whether only these latter patients or all those with significant or subjective shrinkage of tumour were considered, the best prediction of worthwhile response was less than 70 per cent (*Table 3*). This early assessment of tumour size may be improved by ultrasonographic measurement[16].

The ER-ICA gave better prediction of worthwhile response than either clinical assessment.

The prediction of long-term failure to control disease is important. All the methods used predicted immediate progression of disease with certainty but were accurate in only a proportion of those who eventually relapsed or progressed by 2 years. The best discriminant was the ER-ICA, which when low (<20 per cent of cells stained) predicted 60 per cent of women whose tumours were to progress at 2 years. The ER-ICA has the added advantage that it can be performed on a fine-needle aspirate before treatment is started.

Primary tamoxifen therapy is not a substitute for tamoxifen plus appropriate surgery or radiotherapy in elderly women. Appropriateness depends on general fitness and mental state[17]. In patients who are unsuitable for surgical treatment of conventional type, primary tamoxifen therapy is worthy of trial especially in those with detectable tumour ER activity.

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Oesophageal cancer: a population-based study of survival after treatment

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The survival of patients with oesophageal cancer diagnosed during the period 1982–1985 in Nottingham has been studied. Of 496 patients identified from endoscopy, histopathology and hospital activity analysis records, 268 (171 men) lived in the catchment area and had primary oesophageal cancer. Compared with previous studies the proportion of adenocarcinoma (35 per cent) was twice that expected, although survival was similar (hazard rate ratio at 2 years 1·0 (95 per cent confidence interval (c.i.) 0·8–1·4)) whether a squamous cell carcinoma or adenocarcinoma was present. Based on the original treatment intention, surgery was attempted in 34 per cent of cases and was associated with a median survival from diagnosis of 293 (95 per cent c.i. 232–367) days, with 41, 19 and 11 per cent surviving 1, 2 and 3 years respectively. Radical radiotherapy was attempted in 13 per cent of patients and was associated with a median survival of 190 (95 per cent c.i. 136–253) days, with 14, 6 and 6 per cent surviving 1, 2 and 3 years. Intubation alone was performed in 40 per cent of patients, of whom 44 per cent were aged over 75 years and 29 per cent had evidence of metastases, compared with 13 and 11 per cent respectively of those undergoing surgery or radical radiotherapy. The median survival for intubation alone was 100 (95 per cent c.i. 81–122) days, with 6, 3 and 0 per cent of patients surviving 1, 2 and 3 years respectively. Although patients treated surgically had the longest survival, these data indicate that overall survival after any active intervention is modest. Intubation alone is a reasonable option in those not suitable for surgery; randomized trials are needed to compare intubation with new methods of palliation.

Oesophageal carcinoma is a distressing condition with a dismal prognosis fewer than 5 per cent of patients survive for 5 years[1]. There is still no consensus as to the best way to manage the disease[2,3] Among patients with a better prognosis, good results have been achieved in selected series using both radical radiotherapy and surgical resection[4–7]. However, no randomized clinical trials have been reported.

Many patients will unfortunately be suitable only for palliation of dysphagia because of old age, frailty or advanced disease. In recent years the options for palliative treatment have proliferated with the introduction of endoscopic intubation[8] and, more recently, intraluminal radiotherapy[9], laser recanalization[10], bipolar diathermy coagulation[11], and alcohol injection[12].

Until the results of randomized trials become available the effect of current treatment policy on survival remains an important question. This study aimed to assess the survival of all patients with oesophageal cancer from the Nottingham area and to relate survival to the treatment given

Patients and methods

Patients presenting to the Nottingham University and City Hospitals for the first time with oesophageal cancer in the 4-year period 1982–1985 were retrospectively identified from three sources. (1) hospital activity analysis data, (2) histopathology records; and (3) endoscopy unit records This search revealed 496 patients, whose hospital notes were then traced Notes were reviewed by two of the authors (S.E.O. and C S R) and data on treatment and survival recorded on a standard form.

In 31 cases the hospital notes had been lost and information on these patients was thus not available. A total of 112 patients were excluded from analysis because they were referred from outside the Nottingham catchment area (total population 725 000, 355 000 male, 370 000 female). A further 85 patients were excluded because they had a gastric or other non-oesophageal primary tumour (55), or had been diagnosed before 1982 (30) Particular care was taken to exclude patients with endoscopic, radiological or surgical evidence of a primary gastric tumour. Patients with postcricoid oesophageal carcinomas were also excluded A total of 268 patients remained to form the basis of the study.

All but three patients have been followed to death; when hospital follow-up ended, general practice and National Health Service central registry records were consulted for patients' current status.

Statistical analysis

χ^2 statistics were applied to cross-tabulations and the Mann–Whitney *U* test was used to test differences between age distributions because of the marked skew towards the elderly Survival was assessed from the date of clinical diagnosis, which in most cases was also the time of histological diagnosis Hospital mortality was defined as death during the first hospital admission; 30-day mortality was calculated from the date of diagnosis Life-tables were drawn up by the Kaplan–Meier method and differences between survival evaluated by the log rank test[13] Hazard rate ratios with 95 per cent confidence interval (c.i.) were calculated using the Confidence Interval Analysis program, version 1.0 (British Medical Association, London, UK, 1989)

Results

Of the 268 patients identified, 131 (49 per cent) had squamous cell cancer, 95 (35 per cent) adenocarcinoma and 19 (7 per cent) anaplastic cancer. In the remaining 23 (9 per cent) the

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Table 1 *Histological type of oesophageal cancer by primary treatment*

Histological type	No.	Mean age (years)	Metastases evident	Surgery	Radical radiotherapy	Intubation only	Palliative radiotherapy	No treatment
Squamous cell carcinoma	131	69	27 (21)	44 (34)	30 (23)	43 (33)	6 (5)	8 (6)
Adenocarcinoma	95	70	22 (23)	38 (40)	5 (5)	45 (47)	0 (0)	7 (7)
Anaplastic carcinoma and other	19	63	6 (32)	8 (42)	0 (0)	10 (53)	0 (0)	1 (5)
Not known	23	79	4 (17)	2 (9)	0 (0)	8 (35)	1 (4)	12 (52)
Total	268	70	59 (22)	92 (34)	35 (13)	106 (40)	7 (3)	28 (10)

Values in parentheses are percentages

Table 2 *Survival by primary treatment*

Treatment	No.	Mean age (years)	Metastases evident*	Median (95% c.i.) survival (days)	6 months*	1 year*	2 years*	3 years*	4 years*
Surgery	92	65	12 (13)	293 (232–367)	67 (73)	38 (41)	17 (19)	10 (11)	4 (4)†
Radical radiotherapy	35	70	4 (11)	190 (136–253)	18 (51)	5 (14)	2 (6)	2 (6)	0 (0)
Intubation only	106	72	31 (29)	100 (81–122)	29 (27)	6 (6)	3 (3)	0 (0)	—
Palliative radiotherapy	7	66	4 (57)	80 (37–560)	2 (29)	2 (29)	0 (0)	—	—
None	28	77	8 (29)	21 (10–35)	1 (4)	1 (4)	0 (0)	—	—
Total	268	70	59 (22)	146 (114–182)	117 (44)	52 (20)	22 (8)	12 (5)	4 (1)

*Values in parentheses are percentages. c.i., Confidence interval. †One patient died after 5·2 years, three are alive at the end of follow-up 4·5, 4·8 and 5·1 years after diagnosis

histological type of the tumour was unknown. As shown in *Table 1*, patients with adenocarcinoma or squamous cell cancer were of similar ages and the same proportions had evidence of metastatic disease at diagnosis.

Treatment

Many patients underwent combinations of active and palliative treatments. For the purposes of this study patients were categorized according to the primary treatment received (*Table 1*).

In 92 patients (34 per cent), surgery had been performed with the intention of a 'curative' resection, although in 22 this intention was thwarted by the extent of the tumour or by previously undetected metastases.

In 35 patients (13 per cent), a course of radical radiotherapy was started; this was completed in 24. Squamous cell cancer was present in 30 patients, for whom radiotherapy was combined with endoscopic intubation in 21 and surgical intubation in three. Adenocarcinoma was present in the remaining five patients. No patient underwent radical radiotherapy followed by surgery.

In 106 patients (40 per cent) the only active treatment was oesophageal intubation by either surgery (30) or endoscopy (76). A further 55 patients underwent intubation either for recurrent disease or in conjunction with radiotherapy.

Seven patients (3 per cent) received only palliative radiotherapy for metastatic disease. In the remaining 28 patients (10 per cent), no active treatment of the tumour or of metastases was attempted.

As expected, patients undergoing surgery were significantly younger than those having intubation alone ($P < 0·001$), radical radiotherapy ($P < 0·02$) or no treatment at all (*Table 2*). Patients having radical radiotherapy were also younger than those receiving only intubation ($P < 0·05$). Compared with patients undergoing intubation alone, fewer surgical patients had evidence of metastatic disease, and when present this was usually found only at laparotomy ($\chi^2 = 6·7$, 1 d.f., $P = 0·01$). Patients receiving radiotherapy also had less metastatic disease than those undergoing intubation alone ($\chi^2 = 3·6$, 1 d.f., $P = 0·06$).

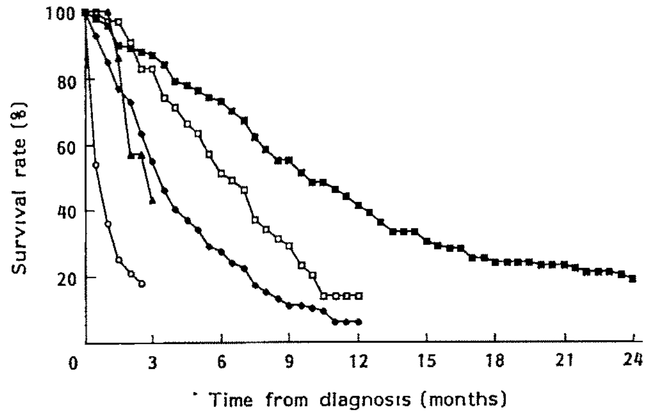

Figure 1 *Survival rate by primary treatment.* ■, *Surgery,* □, *radical radiotherapy,* ◆, *intubation;* △, *palliative radiotherapy,* ○, *no treatment*

Survival by primary treatment (Table 2 *and* Figure 1)

The overall number of patients who survived beyond 2 years was 22 (8 per cent); only four survived for 4 years. Patients undergoing surgery fared significantly better than those receiving radiotherapy (log rank $\chi^2 = 9·8$, 1 d.f., $P = 0·002$) and better than those having only intubation (log rank $\chi^2 = 54·3$, 1 d.f., $P < 0·0001$). Surgery has generally been regarded as the treatment of choice in Nottingham and this is reflected in the small proportion of usually older patients referred for radical radiotherapy. Patients who had a course of radical radiotherapy, including the five with adenocarcinoma, also survived significantly longer than those having intubation alone (log rank $\chi^2 = 7·9$, 1 d.f., $P = 0·005$).

Survival by sex, age, histological type and evidence of metastatic disease (Table 3 *and* Figure 2)

Survival time in univariate analyses was unassociated with sex (hazard rate ratio for men 1·1, for women 1·0; $P = 0·4$) but was inversely associated with increasing age and the presence

Table 3 *Survival by histological type and primary treatment*

	No.	Median (95% c.i.) survival (days)	6 months*	1 year*	2 years*
Squamous cell carcinoma					
Surgery	44	364	35 (80)	21 (48)	10 (23)
Radical radiotherapy	30	182	15 (50)	4 (13)	1 (3)
Intubation only	43	87	5 (12)	2 (5)	1 (3)
Palliative radiotherapy	6	59	2 (33)	2 (33)	0 (0)
No treatment	8	15	1 (12)	1 (12)	1 (12)
Total	131	155 (119–215)	58 (44)	30 (23)	13 (10)
Adenocarcinoma					
Surgery	38	263	28 (74)	14 (37)	7 (18)
Radical radiotherapy	5	242	3 (60)	1 (20)	1 (20)
Intubation only	45	122	17 (38)	2 (4)	1 (2)
No treatment	7	58	1 (14)	1 (14)	0 (0)
Total	95	186 (143–221)	49 (52)	18 (19)	9 (10)
Other histological type	19	81 (24–285)	5 (26)	3 (16)	0 (0)
Unknown histological type	23	30 (11–104)	2 (9)	2 (9)	1 (4)

*Values in parentheses are percentages. c.i., Confidence interval

Table 4 *Early mortality and time spent in hospital by primary treatment*

Treatment	30-day mortality†	Hospital mortality*†	Mean no. of admissions	Median (range) time in hospital (days)	Mean percentage of total survival time spent in hospital
Surgery ($n = 92$)	4	8 (9)	2·9	32 (7–150)	23
Radical radiotherapy ($n = 35$)	1	7 (20)	3·1	53 (6–122)	37
Intubation only ($n = 106$)	16	16 (15)	2·3	22 (3–145)	35
Palliative radiotherapy ($n = 7$)	0	0 (0)	2·3	27 (17–58)	40
None ($n = 28$)	18	15 (54)	1·3	10 (1–75)	60

*Values in parentheses are percentages †Calculated from day of diagnosis to 30 days or during first hospital admission

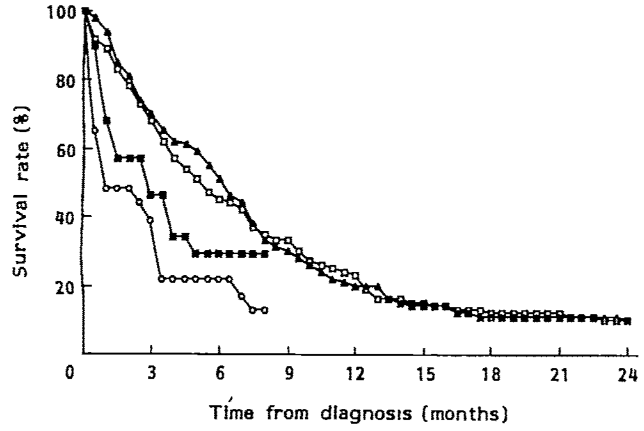

Figure 2 *Survival rate by histological type.* △, *Adenocarcinoma;* □, *squamous cell carcinoma;* ■, *other,* ○, *unknown*

of metastases. Taking patients aged <60 years as the baseline (hazard rate 1·0), the hazard rate was 1·4–1·7 times greater for those aged 60–79 years and 2·3 times greater for those $\geqslant 80$ years ($P < 0{\cdot}01$). Evidence of metastatic disease at diagnosis was associated with a 2·1-fold increase in hazard rate ($P < 0{\cdot}001$).

When survival was analysed by histological tumour type there was no significant increase ($P = 0{\cdot}9$) in hazard rate for adenocarcinoma compared with squamous cell carcinoma, with the hazard rate ratio at 24 months being 1·0 (95 per cent c.i. 0·8–1·4), but the hazard rates were significantly higher for anaplastic cancer and other histological types (hazard rate ratio 1·6, $P < 0{\cdot}01$) and for patients in whom no histology was available (hazard rate ratio 2·2, $P < 0{\cdot}01$).

Early mortality and time in hospital

As shown in *Table 4*, the increased overall survival associated with surgery was not gained at the cost of a high early mortality rate, prolonged hospital stay or repeated hospital admissions. Patients referred for radical radiotherapy spent a median of 53 days in hospital, 21 days longer than those undergoing surgery, and which represented more than one-third of their remaining life.

Discussion

The ideal management of patients with oesophageal cancer continues to be a matter of controversy[2,3]. Although good results using particular methods of treatment are reported[14–18], those for less selected patient groups are not so encouraging[19–22]. To obtain an overall picture of treatment and survival in the Nottingham area, this study identified all patients with oesophageal cancer diagnosed in Nottingham hospitals, including the small number without histological verification. As a consequence this study includes patients in whom no more than minimal investigative effort and treatment were thought appropriate as well as those thoroughly investigated with a view to aggressive therapy. The confounding of treatment option by the degree of investigation precluded satisfactory multivariate analysis of survival by treatment. To exclude selection or referral bias, analysis was confined to patients within the Nottingham catchment area and those referred from other areas were excluded. Patients who never underwent endoscopy or who were not admitted to hospital were not identified, but the number of these untreated patients is likely to be small and their omission has no effect on the figures for survival after treatment.

The proportion of oesophageal adenocarcinomas identified (35 per cent) was twice that anticipated. The study endeavoured to exclude patients with primary gastric cancer and oesophageal infiltration but it is sometimes not possible to state the origin of a tumour even after examination of a resected specimen. Nevertheless, many of the patients identified with adenocarcinoma underwent surgery and were thus least likely to have been misclassified. Furthermore, the total of 268 patients identified is remarkably similar to the number (266) expected from the England and Wales mortality statistics for 1985, in which the crude mortality rates for oesophageal cancer are 112 and 72 per million men and women respectively Other studies have also recently reported an increasing frequency of oesophageal adenocarcinoma. In particular, data from the West Midlands Cancer Registry[20,23] show a rise in the proportion of adenocarcinomas from 6·6 per cent of all oesophageal cancers in 1962 to 23·4 per cent in 1986. This increasing proportion, matched by a fourfold increase in incidence in both sexes, has been seen in tumours of the middle as well as lower third of the oesophagus A recent increase in the frequency of adenocarcinoma has also been reported from Boston, Massachusetts, USA, and from Denmark[24,25].

In Nottingham, as in most UK centres, surgery is the treatment of choice for suitable low-risk patients and the selection bias in favour of this group is evident from the present results. Unfortunately, only 92 patients (34 per cent) were suitable for surgery, in 22 of whom only palliation was possible owing to advanced disease being detected at operation. This accounts in part for the relatively large number of patients (30) who had oesophageal intubation at laparotomy and highlights the need to improve preoperative staging to avoid unnecessary surgery Nevertheless, patients treated surgically had a small but significant survival advantage and probably the best palliation of dysphagia, although no formal grading of the latter was recorded Surgical resection was achieved with a hospital mortality rate of 9 per cent, in keeping with other recently published UK series[26–28]. In addition, surgical patients had a comparatively short postoperative stay with a similar readmission rate to other treatment groups.

However, two-thirds of patients were considered unsuitable for surgery The 30 patients with squamous tumours who were considered fit enough were started on a course of radical radiotherapy. The treatment regimen was reduced if the patient was not tolerating the radical course, and only 20 completed a full course. Seven patients (20 per cent) failed to leave hospital after radiotherapy. Although this treatment was given to a group of poorer prognosis, the results for survival are still disappointing, but again not unlike those of other recent series[29,30] These patients spent approximately 37 per cent of their survival time in hospital and had a similar readmission rate to those undergoing surgery. Whether patients with adenocarcinoma benefit from radiotherapy is still not clear, although there is some evidence of a response in combination with chemotherapy[31]

Endoscopic intubation alone usually results in reasonable palliation if attention is paid to detail. However, even in an experienced centre such as this the hospital mortality rate was 15 per cent. These figures are similar to those in the earlier study of intubation from Nottingham, in which 11 per cent of patients died in hospital and 16 per cent died within 1 month of intubation[8]. The high mortality rate and prolonged hospital stay are a consequence of the type of patient referred for this treatment.

Overall survival rates were poor, with approximately 50, 80 and 90 per cent of all patients having died by 6 months, 1 year and 2 years respectively

There was little difference in survival between squamous tumours and adenocarcinomas, with the overall median survival for squamous cell cancer being 155 days and for adenocarcinoma 186 days. Previous studies have generally found survival to be shorter with adenocarcinoma[24] However, the difference is initially not large and becomes marked only in the few longer survivors. For the West Midlands[20], for example, the age-adjusted survival rates for adenocarcinoma and squamous cell carcinoma were respectively 17 and 20 per cent at 1 year, 7 and 10 per cent at 2 years, 5 and 8 per cent at 3 years, and 1 and 6 per cent at 5 years.

Until recently almost all discussion of the management of oesophageal cancer centred around maximizing survival time. Debate has been dominated by the continuing controversy over the role of radical radiotherapy or surgery for squamous cell cancer As this study emphasizes, this debate is irrelevant to the management of the two-thirds of patients with oesophageal cancer not suitable for surgery. In the past decade the options for palliation have proliferated, with seemingly good results being reported by proponents of each[32] Few properly controlled comparisons have yet been reported Large randomized controlled trials are now urgently needed to establish which of these new treatments or combinations thereof will provide the best palliation, in terms of degree and duration of symptom relief and procedure-related morbidity and mortality rates, without compromising survival.

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Surgical workshop

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Oesophagogastric intramural implantation anastomosis after oesophagectomy

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Oesophagogastric anastomosis is difficult, and high rates of leakage have been reported; such leakage is often fatal$^{1-5}$. This paper describes a mucosa-to-mucosa suture for the inner layer of the oesophagogastric anastomosis, with implantation of the oesophagus into the wall of the stomach. This technique has been used to perform oesophagogastric anastomosis with no leakage or stricture in over 200 patients.

Surgical technique

Carcinoma of the oesophagus

After mobilization of the oesophagus and stomach, the former is divided at the cardia The seromuscular layer is then excised from the fundus of the stomach for a diameter of 4 cm, taking care not to injure the submucosal blood vessels Interrupted mattress sutures are placed 0 5 cm from the cut edge of the seromuscular layer of the stomach, taking care to avoid the mucosa These sutures are placed posteriorly on the oesophagus, well above the planned line of division, and tied The oesophageal muscle coat is now incised circumferentially, 3 cm distal to the sutures The muscularis is then stripped down distally for 1 cm in the submucosal plane and the epithelial layer divided 1 cm distal to the muscular layer. A 2·5-cm incision is made in the gastric mucosa near the front of the exposed area and sutured with interrupted stitches to the cut end of the oesophageal epithelium (*Figure 1*). These sutures are placed 3–5 mm apart and 2–3 mm deep. Stay sutures are inserted in the oesophagus at each end of this first row of sutures

A nasogastric tube and feeding tube can now be passed through the oesophagus into the stomach and the mucosal anastomosis completed The knots are extraluminal The two oesophageal stay sutures may be placed through the seromuscular layer of the stomach at this time (*Figure 2*), when the mucosal suture line is complete the oesophageal end is invaginated into the gastric lumen, clothed in a cape of gastric mucosa Two or three further mattress sutures are applied to the front wall of the oesophagus to approximate the seromuscular layer of the stomach, 3 cm proximal to the mucosal anastomosis The resulting invaginated anastomosis has mucosal and seromuscular suture lines at different levels and generates a flap-valve effect that prevents reflux (*Figure 3*)

Carcinoma of the cardia

The upper part of the stomach is resected, an intestinal clamp applied across the stomach, and the seromuscular layer stripped back for 3 cm on the greater curvature of the stomach The stomach is divided transversely on the greater curve and the resection line then angled downwards on to the lesser curve. The lesser curve is reconstituted with a seromuscular and mucosal suture to create an exposed tube of mucosa 3 cm in length (*Figure 4*) This mucosal tube is used for anastomosis in the manner described above After completion of the anastomosis,

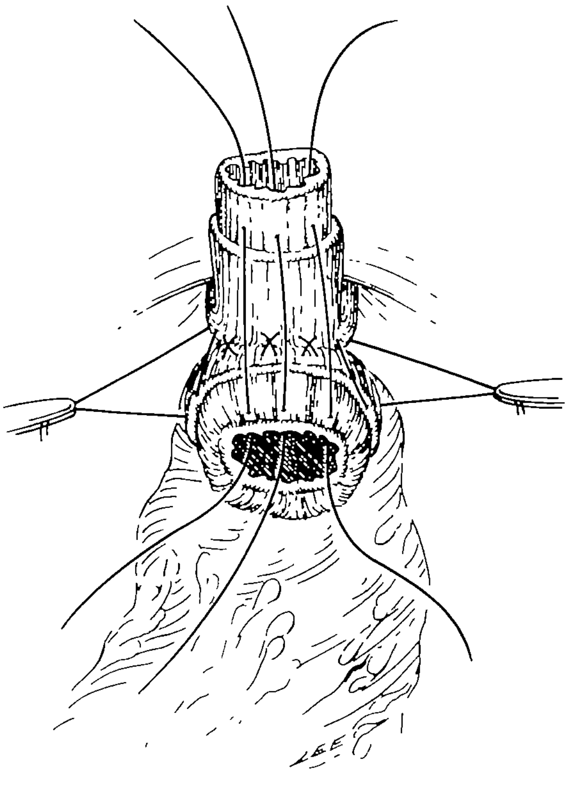

Figure 1 *The posterior seromuscular layer has been completed, 3 cm above the line of division of the seromuscular layer of the oesophagus The epithelial tube is divided 1 cm distal to this and three sutures have been placed between the oesophageal epithelium and the incised gastric mucosa. This layer will be completed by sutures placed between these three sutures*

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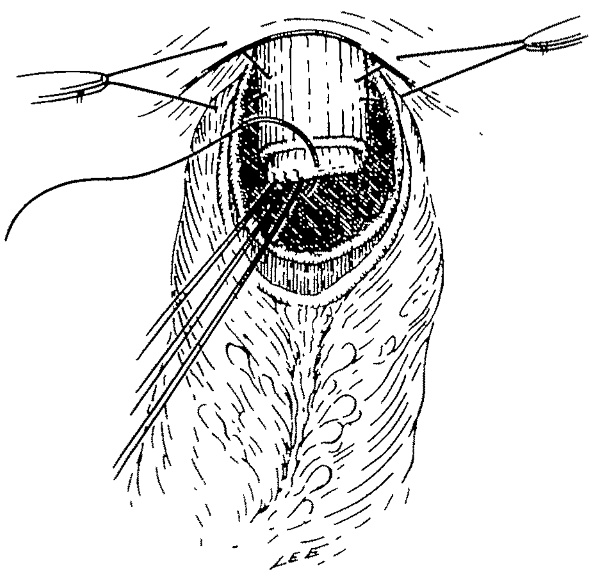

Figure 2 *The anterior mucosal suture line is completed with extramucosal knotting of interrupted sutures. The gastric seromuscular layer is then sutured to the oesophageal muscle 3 cm above its point of division*

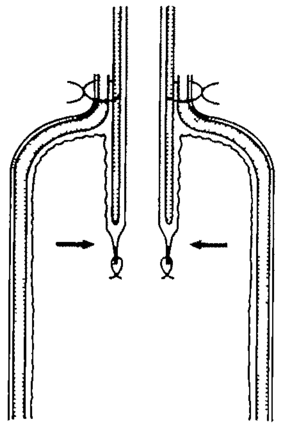

Figure 3 *The completed anastomosis the invaginated mucosal anastomosis and distal oesophagus, which acts as flap-valve to prevent reflux (arrows). The wide separation of the seromuscular and mucosal anastomoses ensures sound healing without leakage*

a reinforcing suture is applied at the junction with the lesser curvature suture line.

Discussion

The incidence of anastomotic leakage after resection of oesophageal and cardiac cancer is 3–19 per cent. Leakage has a mortality rate of 39–94 per cent[1–5] This technique brings together a large area of the submucosa of the oesophagus and the stomach. These have a rich blood supply, so healing is rapid; furthermore, apposition of the gastric submucosa and the oesophageal muscle contributes to secure healing.

Suture of the seromuscular layer of the stomach to the oesophageal muscularis and surrounding tissues isolates the anastomosis from the pleural cavity and reduces the tension on the mucosal anastomosis. Stricture may occur in 9 per cent of cases[6]. Aetiological factors include oversewing, crushing by the clamp, poor apposition and local infection. We use about 20 fine silk stitches to ensure good apposition between the two layers of mucosa. Histological examination shows slight proliferation of fibrous tissue, and stricture at the anastomosis was rarely found in this series. The mucosal anastomosis and the oesophageal and gastric muscular layers are on three different levels (*Figure 3*), which appears to avoid contraction of an annular scar at the anastomosis. Examination using barium meal after 6 months showed that contrast passed freely through the anastomosis, which maintained a diameter of 1·2–2 cm.

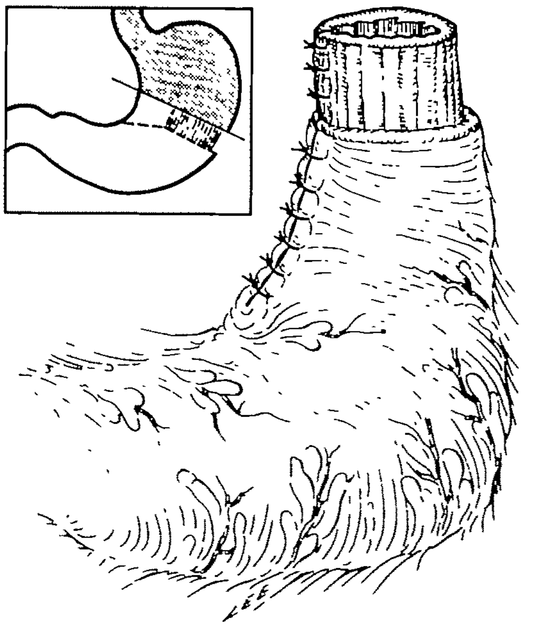

Figure 4 *The prepared gastric mucosal tube after oesophagogastrectomy. The lesser curve is reconstituted by a full-thickness mucosal suture to leave an exposed tube of gastric mucosa 3 cm in length and 4 cm across*

Reflux of gastric juice may be prevented by invagination of 2–3 cm or more of oesophagus into the stomach[7,8]; in this series, the oesophagus was invaginated into the stomach for 3 cm or more. As the pressure in the stomach increases, the oesophagus would be closed by the pressure. This was confirmed in some patients by barium meal studies.

This technique has been used in 225 patients; there has been no anastomotic leakage after operation. This procedure prevents reflux of gastric juice into the oesophagus, and we believe it to be a safe and reliable method for oesophagogastric reconstruction.

Acknowledgements

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Autotransplantation of splenic tissue in an isolated segment of small intestine

The ability of splenic tissue to regenerate when implanted in an isolated segment of small intestine with intact circulation was studied in six pigs. After total splenectomy, 10 per cent of the weight of the spleen was implanted in a 10–15-cm long isolated segment of small intestine with an intact vascular supply. Bowel continuity was established by end-to-end anastomosis. Before implantation, the mucosal layer was completely removed from the isolated segment of the small intestine. The animals were killed 6 months later and the isolated segment of small bowel containing the splenic tissue identified. Most of the implanted splenic tissue was recovered in the isolated segment of small intestine; the weight ranged from 43 to 120 (mean 80) per cent of that of the implanted tissue. An isolated segment of small intestine with an intact circulation produces a higher index of regeneration than other previously reported sites.

Splenectomy causes a life-long risk of developing fatal overwhelming postsplenectomy infection[1,2]. Splenic preservation after injury protects against this complication and is the treatment of choice for most surgeons[3–5]. In the case of unavoidable splenectomy, autotransplantation of splenic tissue has been recommended[6–8]. Different sites and methods of autotransplantation have been studied. Autotransplantation of approximately 40 per cent of the weight of intact spleen in an omental pouch results in better regeneration and survival in rats than implantation of more or less splenic tissue[9–11]. Implantation of sliced rather than minced splenic tissue in multiple small omental pouches rather than in a single large pouch results in significantly better regeneration in rabbits[12,13]. To improve the results of splenic autotransplantation, the present study was undertaken to investigate the regenerative capacity of implanted splenic tissue in an isolated segment of the small intestine with an intact circulation.

Materials and methods

Six female Danish Landrace pigs weighing 28–32 kg were studied. Before surgery the animals were fasted for 12 h, with free access to water. Laparotomy was performed through a midline incision under halothane–nitrous oxide–oxygen anaesthesia. The abdomen was explored for the presence of accessory splenic tissue. A 10–15-cm long segment of proximal jejunum was isolated on its mesentery (i.e. with intact circulation). Bowel continuity was re-established by end-to-end anastomosis and the defect in the mesentery sutured. The mucosal layer was removed from the isolated segment of small intestine. The spleen was removed and weighed. Next, 10 per cent of the spleen was cut into thin slices 2–3 mm thick and implanted evenly in the prepared isolated seromuscular loop of small intestine. The ends of the isolated bowel segment were closed. To prevent accumulation of the tissue of the slices over other slices in the bowel segment, three or four absorbable 4/0 sutures were set between the implanted slices to form partly separated pockets of small intestine. The bowel segment was fixed to the nearby small intestine to prevent torsion of its vascular pedicle.

Pigs were killed 6 months later under general anaesthesia. The isolated segment of small intestine containing the splenic tissue was identified. Regenerated splenic tissue was removed, weighed, and portions fixed in formalin for microscopic examination. The morphology of the transplanted tissue was compared with that of samples from six normal control animals using the method of Gordon and Sweet for reticulin[14].

Results

All the animals survived surgery and gained weight compared with non-transplanted pigs of similar age. No episode of infection was observed during the 6 months of observation after transplantation.

Table 1 shows the body-weight, weight of spleen, amount of splenic tissue and number of slices implanted in the isolated segment of small intestine, and amount of tissue and number of slices recovered 6 months later.

No haematoma or abscess was encountered in the isolated bowel segment, its mesentery or elsewhere. Intra-abdominal adhesions were negligible and none was observed around the implanted splenic tissue. Implanted slices of splenic tissue regenerated perfectly in most of the animals. In one pig the recovered amount was more than that implanted. All the regenerated slices were surrounded by the thin seromuscular layer of the small intestine, which on gross examination resembled the splenic capsule (*Figure 1*).

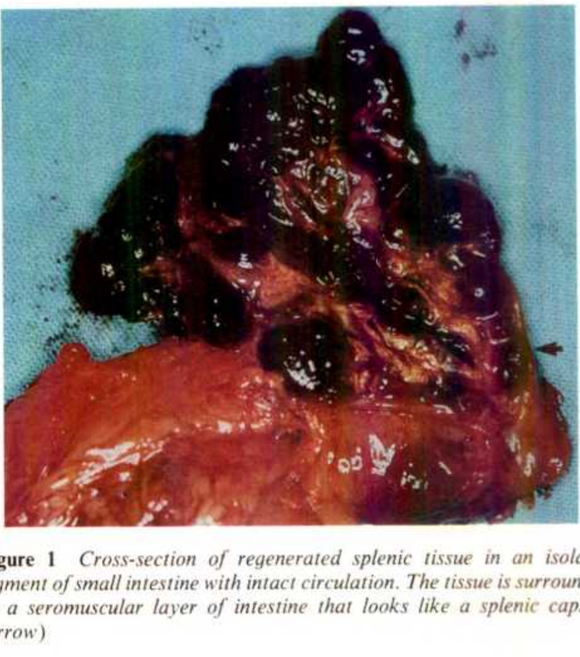

Figure 1 *Cross-section of regenerated splenic tissue in an isolated segment of small intestine with intact circulation. The tissue is surrounded by a seromuscular layer of intestine that looks like a splenic capsule (arrow)*

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Table 1 *Outcome 6 months after autotransplantation of spleen in an isolated segment of small intestine with intact circulation in pigs*

Animal no.	Body-weight (kg)	Weight of intact spleen (g)	Weight of spleen implanted (g)	No. of slices implanted	Weight of spleen recovered (g)	No. of slices recovered
1	30	100	10	24	12 (120)	24 (100)
2	30	72	7	14	3 (43)	9 (64)
3	32	110	11	28	9 (82)	24 (86)
4	28	88	9	23	6·5 (72)	15 (65)
5	32	70	7	23	5 (71)	18 (78)
6	30	90	9	24	6·5 (72)	18 (75)
Mean	30·3	88·3	8·8	22·7	7·0 (80)	18 (79)

Values in parentheses are percentages

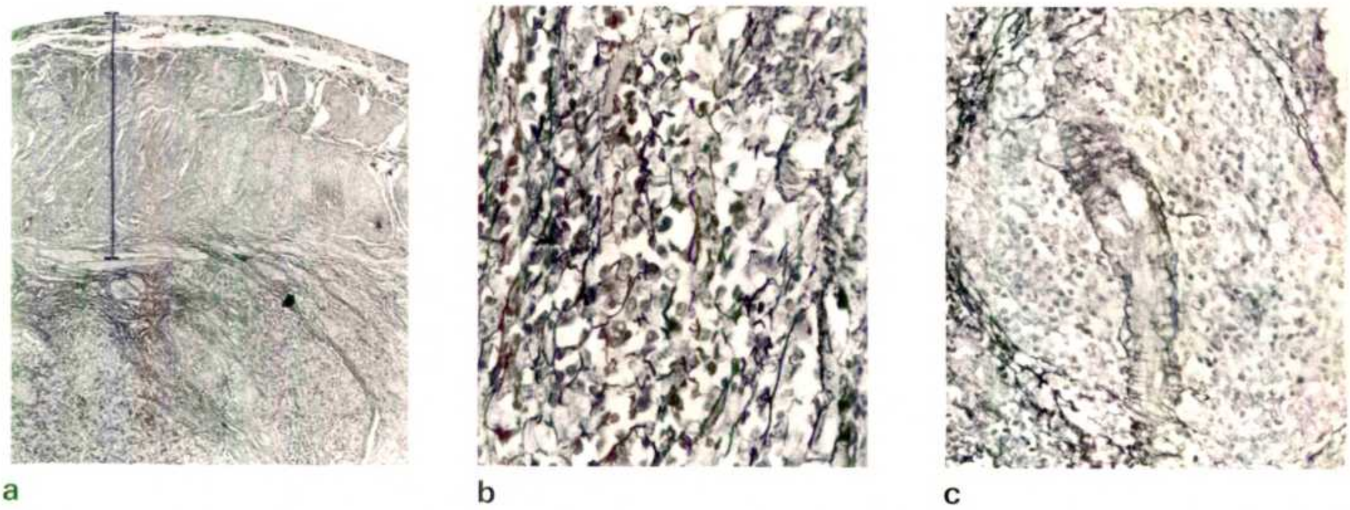

Figure 2 **a** *Low-power view of splenic tissue autotransplanted in a segment of the small intestine. The bar shows the thickness of the smooth muscle coat and the serosa of the bowel wall. (Original magnification × 4).* **b** *Red pulp of autotransplanted splenic tissue with sinusoids supported by reticulin meshwork. (Original magnification × 20).* **c** *White pulp of autotransplanted splenic tissue. Lymphoid tissue is aggregated around an obliquely cut central artery. (Original magnification × 20)*

A mean of 79 per cent of the implanted splenic slices regenerated. The weight of recovered splenic tissue was 43–120 (mean 80) per cent of the weight of that implanted. In pig 2 a few calcified foci were seen between the regenerated splenic slices, denoting complete degeneration. In the same pig the regeneration of the three residual slices was much less than in the other animals.

The histomorphological appearance of the autotransplanted spleen did not differ from that of the control tissue (*Figure 2*). The overall architecture was well preserved. The amount and structural appearance of red and white pulp, with occurrence of sinusoids (red pulp) and germinal centres (white pulp), were the same as in control tissue.

Discussion

This study shows regeneration of splenic tissue autotransplanted in an isolated segment of small intestine with intact circulation. With other sites and techniques of splenic autotransplantation, the circulation to regenerated splenic tissue is established through capillaries. In the present method a much larger arterial supply and venous drainage in the mesentery of the isolated bowel loop supplies the regenerating tissue.

One of the most important factors in the function of the spleen is an intact circulation[15] for efficient clearing of bacteria. This new method may be superior to other techniques. After autotransplantation of splenic tissue into an omental pouch, the circulation to the regenerating tissue has been estimated to be 1–2 per cent of normal[8]. This may account for the occurrence of overwhelming postsplenectomy infection in patients in whom regenerated splenic tissue has been found at autopsy[16].

Implantation of splenic tissue in omental pouches produces adhesions, making further surgery in these patients more difficult but, with the splenic tissue confined to a closed loop of small intestine, this new technique should produce no more adhesions than a laparotomy.

Better vascularization was confirmed by histological findings of intact overall architecture and a normal relationship between red and white pulp with normal intracompartmental structure.

This new site for autotransplantation of splenic tissue is ideal for further studies of the immunology of autotransplantation and regeneration. Such studies should be carried out before the technique can be advocated for clinical trial.

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Prospective study in adults of splenic preservation after traumatic rupture

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Seventy-five adults with splenic injury were evaluated prospectively over 45 months to examine the possibility of splenic preservation. Haemodynamically unstable patients underwent surgery with the intent of splenic preservation. Stable patients received non-operative treatment regardless of the grade of splenic injury determined by ultrasonography and computed tomography. Thirty-seven patients required splenectomy and in 38 the organ was preserved (20 operative preservation, 18 non-operative treatment). Of 22 patients initially receiving non-operative treatment, there were four secondary haemorrhages after 7, 7, 10 and 13 days making surgery necessary. Three of these patients underwent splenectomy and in one the spleen was preserved by partial resection. After splenectomy four patients required reoperation because of rebleeding or for evacuation of a haematoma. Patients who had undergone splenectomy had a significantly increased infection rate ($P < 0{\cdot}005$) *compared with those in whom the spleen was preserved, even when patients were matched with respect to multiple trauma using the Injury Severity Score* ($P < 0{\cdot}01$).

The overwhelming postsplenectomy sepsis syndrome[1] was first described in 1952. Higher infection rates in children and adults[2–4] and haematological disturbances[3,4] after splenectomy have since been recognized. This has led to attempts at splenic autotransplantation[5–7] and splenic preservation *in situ*[8–22]. Autotransplantation has been shown experimentally[18,20,21] and clinically[21,23–25] to be of little value; organ preservation *in situ* is, in contrast, increasingly advocated and appears to be safe[8–11,13]. There have recently been reports of partial splenic resection after trauma[8–11].

Improved diagnostic facilities, better knowledge of the methods of non-operative treatment in adults[12,22], and close follow-up have led to an increasing number of splenic preservation procedures. In this study, different diagnostic and therapeutic regimens after splenic injury were evaluated prospectively and early complication rates compared.

Patients and methods

Between October 1986 and June 1990, 75 patients (18 women, 57 men; mean age 35 (range 16–78) years) with splenic injuries from blunt abdominal trauma were studied prospectively. Haemodynamic status on admission was used to determine the choice of treatment. Stable patients received non-operative treatment; unstable patients underwent splenorrhaphy, partial splenic resection or splenectomy.

In stable patients with a shock index (pulse rate/systolic blood pressure) < 1 on admission and an initial stable phase (< 2000 ml electrolyte solution and/or < 2 units packed red cells administered) of at least 2 h a conservative approach was adopted. Ultrasonography and/or computed tomography (CT) were used for accurate assessment of the severity of splenic and concomitant injuries. Peritoneal lavage was used in patients who required operative procedures for extra-abdominal injuries because it could be repeated in theatre if the patient became clinically unstable. It was employed in a few patients when ultrasonography was not immediately available. On the basis of the ultrasonography, CT and/or intraoperative findings, the splenic injury was graded I–V (*Table 1*). The severity of multiple trauma was assessed using the Injury Severity Score (ISS).

Patients unsuitable for non-operative treatment underwent laparotomy with the intention of splenic preservation by splenorrhaphy or partial resection. The decision was left to the operating surgeon.

The surgical technique of splenic preservation has been described in a technical protocol[26] and recorded in a videotape[27]. The hilum was clamped with a soft bowel clamp and methods for repair depended on the grade of injury. Resorbable collagen platelets, resorbable gauze, polytetrafluoroethylene strips and a variety of methods to achieve haemostasis (infra-red photocoagulation, haemostatic material and supportive mesh) were used. In patients undergoing partial resection with lower pole injuries extending into the hilum, the spleen was preserved on the short gastric vessels with or without preservation of an upper pole artery. The variable anatomy of the arteries at the hilum determined the type of resection[16] (*Figure 1*).

Single-dose antibiotic prophylaxis with 2 g cephazolin was given immediately before surgery. In patients undergoing splenectomy, cephazolin was continued for 3–5 days (1 g four times daily), when one dose of benzathine benzylpenicillin ($2{\cdot}4 \times 10^6$ units) was given intramuscularly. Polyvalent *Pneumococcus* vaccine was given on the tenth day after operation. Antibiotics were otherwise given only for proven infections.

All patients were assessed for early infection and only those with pathognomonic clinical and radiological findings supported by positive bacteriological culture were included. Identical bacteriological surveillance was undertaken in all groups.

Statistical analysis was performed using the χ^2 test.

Results

Diagnosis of intra-abdominal trauma with suspected splenic injury was made by ultrasonography in 44 patients and by CT in 20. Peritoneal lavage was carried out in 22 patients and in four laparotomy was performed on clinical grounds. The diagnosis and grading of splenic injury in patients receiving non-operative treatment was made by CT in 16 and by ultrasonography in six, the latter mainly with minor injuries of grades I and II, where ultrasonography seemed reliable and

Table 1 *The Splenic Injury Scale*

Grade	Injury
I	Subcapsular haematoma
II	Capsular tear
IIIa	Superficial parenchymal tear (< 1 cm)
IIIb	Deep parenchymal tear (> 1 cm) without involvement of hilum
IV	Parenchymal tear with involvement of hilum
V	Fragmentation

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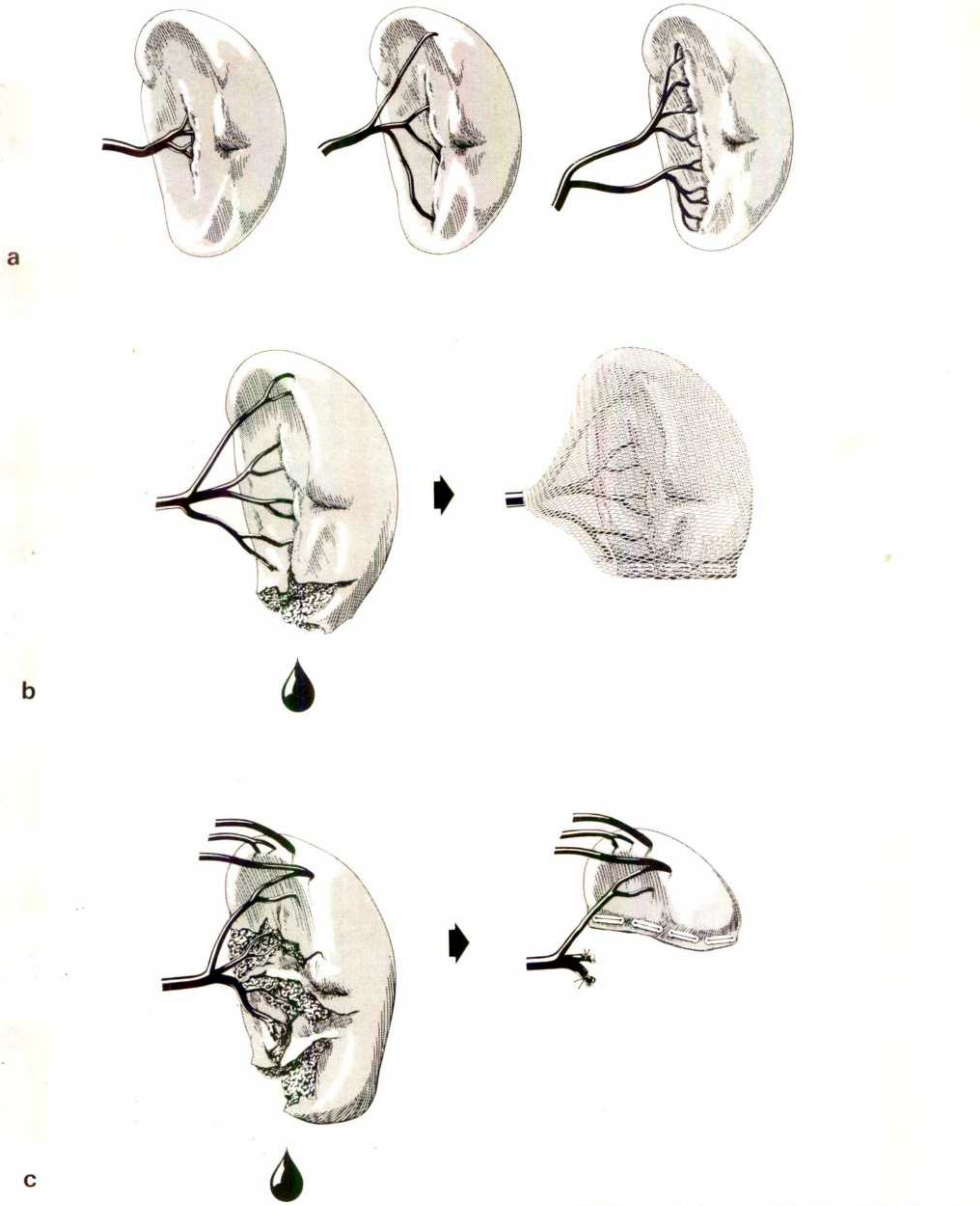

Figure 1 **a** *Variable anatomy of the arteries to the hilum and two types of partial splenic preservation of the upper pole* **b** *with a mesh and* **c** *on an upper pole artery and the short gastric vessels*

sufficient. Follow-up of all patients treated conservatively was by repeated CT examination.

The management of the 75 patients is shown in *Figure 2*. A total of 37 patients required splenectomy, 34 performed primarily and three secondarily. In 22 patients, primary treatment was non-operative. Secondary bleeding occurred after 7, 7, 10 and 13 days in four such patients, three of whom underwent splenectomy. The fourth patient underwent partial splenic preservation. A total of 38 spleens were preserved, 18 without operation and 20 following surgery. In 13 patients the spleen was preserved as a whole and in seven partial resection was necessary. In three patients, only the upper pole of the spleen was preserved, in two supplied only by the short gastric vessels and in the third by the upper pole artery (*Figure 1*). Partial splenic resection was performed in one grade II, two grade III, three grade IV and one grade V injuries. The mean increase in the operative time for preservation measured from clamping of the vessels at the hilum until repositioning of the spleen in the subdiaphragmatic cavity was 18 (range 9–26) min.

There were nine complications from bleeding. Four were

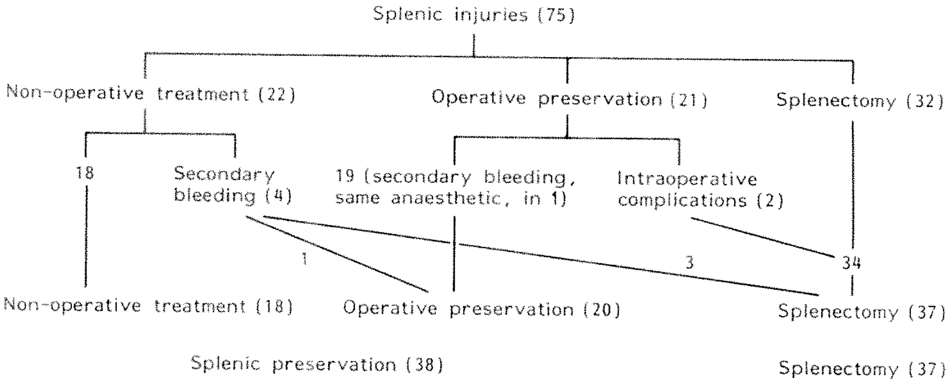
Splenic injuries (75)
Non-operative treatment (22)
Operative preservation (21)
Splenectomy (32)
18
Secondary bleeding (4)
19 (secondary bleeding, same anaesthetic, in 1)
Intraoperative complications (2)
1
3
34
Non-operative treatment (18)
Operative preservation (20)
Splenectomy (37)
Splenic preservation (38)
Splenectomy (37)

Figure 2 *Treatment of 75 patients with splenic trauma*

Table 2 *Infections and their causative organisms in patients with splenic trauma*

Treatment	Infection	Organism
Splenectomy (15)	Respiratory tract (10)	*Haemophilus influenzae* (5) *Staphylococcus aureus* (2) *Enterobacter* (2) *Klebsiella* (2) *Proteus mirabilis* *Pseudomonas aeruginosa* *Citrobacter* *Serratia marcescens* *Pneumococcus*
	Sepsis (4) (positive blood culture)	*Pseudomonas aeruginosa* (2) Enterococcus (*Streptococcus faecalis*) (2) *Klebsiella*
	Infected abdominal haematoma (2)	*Serratia marcescens* *Pseudomonas aeruginosa* *Actinobacter* Enterococcus (*Streptococcus faecalis*) *Proteus mirabilis*
	Urinary tract (1)	*Escherichia coli*
Operative preservation (2)	Respiratory tract (1)	*Haemophilus influenzae*
	Urinary tract (1)	*Staphylococcus epidermidis*
Non-operative (2)	Respiratory tract (2)	*Haemophilus influenzae* *Pseudomonas cepacia* *Staphylococcus aureus*

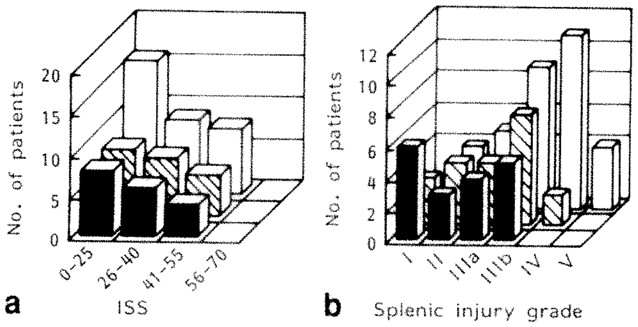

Figure 3 **a** *Injury Severity Score (ISS) and* **b** *splenic injury grade for patients undergoing non-operative treatment* (■), *operative preservation* (▨) *or splenectomy* (☐) *for splenic trauma*

the secondary splenic ruptures in patients receiving non-operative treatment. In one patient undergoing partial splenic resection, rebleeding occurred immediately after closure of the abdomen; this was treated by immediate reoperation. Four rebleeds after splenectomy were from the splenic bed; no patient requiring reoperation suffered a complication as a consequence. Two patients developed a pancreatic fistula after splenectomy but both settled with conservative treatment within a few days.

Septic and infective problems are shown in *Table 2*. The infection rate was significantly lower in patients undergoing splenic preservation (four of 38 *versus* 15 of 37 patients having splenectomy, $P < 0{\cdot}005$). After matching patients for ISS, 12 proven infections occurred in 33 submitted to splenectomy compared with four of 38 having splenic preservation ($P < 0{\cdot}01$).

Five patients in the series died: three after splenectomy and two after operative preservation. Two patients died after splenectomy from acute respiratory distress syndrome (ARDS) and one from a cerebral injury. Of the patients with splenic preservation, one died from ARDS and the other from a pulmonary embolus.

Details for all 75 patients divided into the different treatment groups according to ISS and grade of splenic injury are shown in *Figure 3*.

Discussion

There is increasing evidence of a raised late mortality rate after splenectomy[2–4], but early complications after splenic injury have rarely been studied[2,28].

The present study demonstrates the ability to preserve an increasing number of traumatized spleens in adults by surgical preservation or non-operative therapy. This strategy has previously been used mainly in children[11,13,16]. This change has occurred through increasing experience with operative preservation and an ability and confidence to pursue a non-operative approach based on accurate diagnostic methods[22].

In haemodynamically unstable patients, operative preservation is the treatment of choice. Partial resection is employed in cases where the lower pole of the spleen is more traumatized because of its relatively exposed position. An upper pole artery is present in about 60 per cent of patients[29,30], making upper pole splenic preservation technically feasible (*Figure 1*).

Splenic preservation is a safe technique[8-13,18,20-22,29], as this study confirms; there are no more bleeding complications than after splenectomy. A small number of patients treated without operation develop secondary bleeding. In the present series this occurred in four of 22 patients receiving primary non-operative treatment. Patients in the group so treated who developed secondary rupture were all older than 40 years and the non-operative approach may not be so safe in those over this age. The secondary rupture is often dramatic, requiring immediate surgery; most occur within the first 2 weeks following injury[12,18].

All patients treated without operation should be kept in hospital for at least 10 days and routine ultrasonography or CT carried out before discharge. If there is persisting intra-abdominal fluid collection, additional CT with intravenous contrast should be performed. The patient should not play strenuous sports for at least 3 months and must report immediately if there is sudden left upper abdominal pain. Relatives and general practitioners should be similarly informed. Some 3–6 months after injury, further ultrasonography and/or CT should be carried out.

In this series even when patients were matched for ISS there was a significant difference in the rate of early postoperative infections, which were caused by capsulated bacteria (*Table 2*).

In view of the early complications after splenectomy demonstrated by the present study and others[2,28], and the late complications[1-4,14,17,18,20,21], preservation is the treatment of choice for splenic trauma. The increase in operating time is minimal. Non-operative treatment may be valuable in younger patients with limited injuries. Experienced teams should be able to preserve the spleen in 60–80 per cent of all patients.

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Surgical workshop

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Laparoscopic splenectomy

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New laparoscopic procedures continue to be described$^{1-5}$ as instruments such as the Endo-GIA stapler (Auto Suture, Lyons, France) allow intestinal and vascular transection and closure. Laparoscopic splenectomy, including a method for extracting the spleen, is described below.

Surgical technique

Splenectomy was carried out in a 17-year-old female patient with autoimmune thrombocytopenic purpura in September 1991. The disease was corticosteroid dependent with enhanced platelet destruction. Following the administration of 100 mg prednisone daily, the platelet count rose from 20×10^9/l to 145×10^9/l the day before surgery.

The surgeon stood between the patient's legs, the first assistant on the left side and the second on the right. The laparoscope with videocamera was inserted in the upper part of the umbilicus. Four other cannulas were inserted (*Figure 1*). The stomach was retracted to the right with an atraumatic forceps and the splenogastric ligament exposed. Inferior polar splenic vessels and inferior short gastric vessels were divided between clips. The inferior part of the splenogastric ligament was opened using electrocoagulation and clips. When the lower part of the spleen was free, it was gently raised, revealing the splenic vessels and tail of the pancreas. An Endo-GIA stapler was placed around these vessels and three staples were used to divide the hilum. The upper short gastric vessels were divided between clips; the posterior peritoneal attachments were cut using electrocoagulation. The free spleen was placed in a plastic bag inserted via the left 12-mm cannula. The opening of the bag was pulled out through the left abdominal skin incision after removal of the cannula. The spleen was cut into fragments inside the bag, with standard scissors and forceps, and the fragments removed through the opening of the bag. The procedure took 5 h.

No blood or platelet transfusion was required. The patient was discharged 6 days after operation with a platelet count of 1100×10^9/l.

This procedure has since been repeated in a second patient, with an uneventful postoperative course.

Discussion

The Endo-GIA stapler allows intestinal and vascular transection and closure. The plastic bag method avoids intra-abdominal loss of spleen fragments. Laparoscopic splenectomy may be associated with operative problems and the surgeon should be experienced in endoscopic and abdominal surgery. The operation should probably also be restricted to patients with haematological disease not associated with splenomegaly (i.e. idiopathic thrombocytopenic purpura).

A reduced incidence of subphrenic and wound abscesses or wound dehiscence is a potential advantage of the endoscopic method. Cosmetic advantages, faster recovery with less postoperative pain, and reduced hospital stay and costs are also expected.

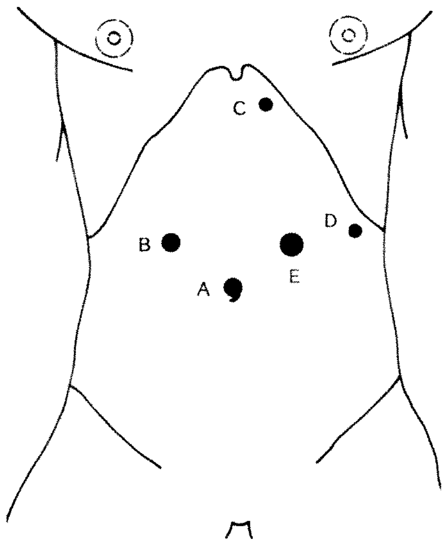

Figure 1 *Positions of ports for laparoscopic splenectomy. A, 10-mm cannula for monocular endoscope with videocamera; B, 10-mm cannula for atraumatic grasping forceps to hold the stomach; C, 5-mm cannula for aspiration–irrigation instrument; D, 5-mm cannula for atraumatic forceps; E, 12-mm cannula for Endo-GIA stapler*

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Ascaris-induced acute pancreatitis

The incidence, clinical disease and outcome of acute pancreatitis caused by ascariasis in an endemic area of Kashmir, India, was studied prospectively. Ascariasis was an aetiological factor in 59 of 256 patients (23·0 per cent) with acute pancreatitis. Worms had invaded the bile duct in 51 patients, the pancreatic duct in four and both ducts in four. Pancreatitis was mild in 46 patients and severe in 13. Associated pyogenic cholangitis was present in eight. Acute complications occurred in 11 patients. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in all cases within 72 h of admission and delineated ascarides in the duodenum invading the ampullary orifice (44 patients), in the bile duct (55) and in the pancreatic duct (eight). At ERCP, worms were extracted from the ampullary orifice and removed via the mouth of 33 patients with intractable epigastric pain, leading to rapid relief of symptoms. The eight patients with pyogenic cholangitis underwent endoscopic nasobiliary drainage to decompress the bile ducts; worms were extracted from the bile duct of three of these patients using a Dormia basket. A total of 56 patients recovered from acute illness with a combination of conservative and endoscopic treatment; the other three required emergency surgery. At a mean(s.d.) follow-up of 19(7) months, ten patients showed symptomatic worm reinvasion of the biliary tree. The overall mortality rate was 3 per cent.

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Ascaris lumbricoides is the most common helminth worldwide, and ascariasis is recognized as one of the less common causes of acute pancreatitis. Such pancreatitis occurs by direct worm invasion of the pancreatic duct (pancreatic ascariasis), by worm invasion of the ampullary orifice, entering the bile duct and blocking the pancreatic duct orifice (biliary ascariasis), and by worm invasion of both the bile duct and pancreatic duct (biliary and pancreatic ascariasis). Although biliary ascariasis is a known cause of pancreatitis[1–3], the fact that the literature contains only a few isolated reports of pancreatic ascariasis demonstrates its rarity[4–6]. Moreover, the present knowledge of *Ascaris*-induced acute pancreatitis is scanty and an adequate description of the clinical disease and outcome is lacking.

Kashmir in India is an area in which ascariasis is endemic: in a recent survey the prevalence was 30 per cent of adults and 60 per cent of children[7]. Ascariasis here is as frequent a cause of symptomatic adult biliary disease as gallstones[1]. In this paper 59 patients with *Ascaris*-induced acute pancreatitis are reported, including eight with pancreatic invasion, who were prospectively studied for clinical disease and outcome. Endoscopic extraction of worms from the duodenum and across the ampullary orifice as a part of the overall management is highlighted.

Patients and methods

From June 1986 to December 1991, 256 patients were admitted with a diagnosis of acute pancreatitis based on a serum amylase level >800 units/l and a compatible clinical picture. Patients with acute exacerbation of chronic pancreatitis were not included in this study. Ultrasonography of the liver, biliary tree and pancreas was carried out using a real-time scanner (Aloka SSD256; Aloka, Tokyo, Japan) within 24 h of admission and thereafter every 24–48 h to detect complications. The sonographic diagnosis of biliary or pancreatic ascariasis was made when non-shadowing long echogenic structures with a central sonolucent tube were visualized in the biliary tree or pancreatic duct. Endoscopic retrograde cholangiopancreatography (ERCP) using a side-viewing duodenoscope (JFB3 or JFIT-10; Olympus Optical, Tokyo, Japan) was carried out within 72 h of admission in patients with suspected biliary or pancreatic ascariasis on the basis of the clinical or ultrasonographic criteria previously described[8]. From April 1989, all patients with severe pancreatitis underwent enhanced computed tomography on admission and at intervals thereafter. Severity of pancreatitis was predicted according to the criteria of Imrie *et al.*[9]; the attack was predicted to be mild if the prognostic score was 0–2 and severe if 3–8.

Acute pancreatitis was considered to be caused by *A. lumbricoides* infection when adult worms were detected in the biliary tree and/or pancreatic duct at ultrasonography and/or ERCP. The aetiology of acute pancreatitis was as follows: gallstones, 112 (43·8 per cent); ascarides, 59 (23·0 per cent); other, ten (3·9 per cent); and undefined, 75 (29·3 per cent). A passing reference to some of these patients has been made in an earlier report[10].

Results

The study group comprised six children and 53 adults (34 women, 19 men) of mean(s.d.) age 34(10) (range 8–61) years. Of these, 51 had biliary ascariasis, four had pancreatic involvement, and four had invasion of both biliary and pancreatic systems. The biliary tree contained a single worm in 18 patients, two worms in 24 and three or more in 13. The pancreatic duct was invaded by a single worm in seven patients and by four worms in one. Upper abdominal pain referred to the back of duration 1–6 days and vomiting were typical presenting symptoms (*Table 1*). Cholangitis, defined as a symptom complex of high fever with rigors, jaundice and upper

Table 1 *Clinical features of* Ascaris-*related acute pancreatitis in 59 patients*

	No. of patients
Abdominal pain	59 (100)
Back pain	44 (75)
Nausea and vomiting	52 (88)
Roundworms in vomitus	50 (85)
Fever	17 (29)
Jaundice	15 (25)
Tender hepatomegaly	23 (39)
Gallbladder lump	8 (14)
Decreased bowel sounds	8 (14)

Values in parentheses are percentages

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Table 2 *Morbidity and mortality in 59 patients with* Ascaris-*related acute pancreatitis with respect to the site of worm invasion into the bile duct and/or pancreatic duct*

	Site of invasion		
	Biliary tree alone ($n = 51$)	Pancreatic duct alone ($n = 4$)	Both ducts ($n = 4$)
Duodenal ascarides invading ampullary orifice	40	0	4
Severity of pancreatitis			
Mild	41	4	1
Severe	10	0	3
Complications*	8	0	3
Pseudocyst	3	0	0
Renal failure	2	0	1
Respiratory failure	3	0	1
Shock	5	0	2
Disseminated intravascular coagulation	1	0	0
Death	1	0	1

*Four patients had two or more complications

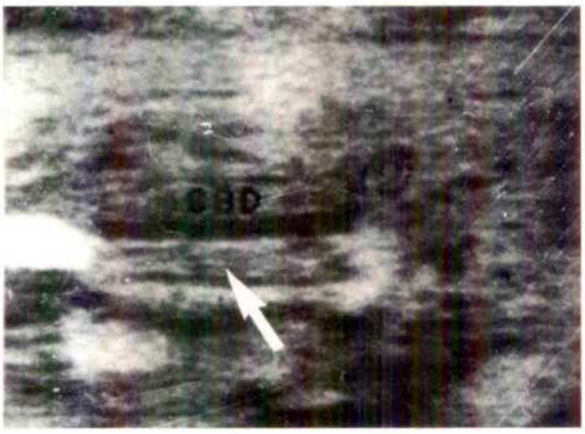

Figure 1 *Ultrasonography revealing a thick long non-shadowing echogenic strip (arrow) containing a central sonolucent tube, representing the digestive tract of the roundworm, within the dilated common bile duct (CBD)*

abdominal pain or tenderness, was present in eight patients. Peritoneal aspirate produced haemorrhagic fluid in two.

Acute pancreatitis was predicted to be mild in 46 patients (78 per cent) and severe in 13 (22 per cent) (*Table 2*). All four patients with pancreatic ascariasis had a mild attack, whereas three of the four with biliary and pancreatic invasion had severe pancreatitis. The prevalence of severe pancreatitis in patients with biliary ascariasis was 20 per cent. Nine of the 13 patients with a severe attack had three or more worms in the biliary tree. The complication rate among those whose pancreatitis was predicted to be mild was 15 per cent compared with 39 per cent of patients predicted to have a severe attack.

Laboratory findings

Stool examination revealed ova of *A. lumbricoides* in all patients. The mean(s.d.) serum bilirubin level was 29(14) (range 17–53) μmol/l. The serum bilirubin level was $\leqslant 17$ μmol/l in 26 patients, 18–34 μmol/l in 18 and > 34 μmol/l in 15. Serum alkaline phosphatase was raised to a mean(s.d.) concentration of 820(210) (range 580–1140) units/l in 45 patients, all of whom had worm invasion of the biliary tree. Serum amylase levels ranged from 900 to 4160 (mean(s.d.) 1600(272)) units/l. Blood cultures were taken from 25 patients, eight yielding micro-organisms: *Escherichia coli* in six and *Klebsiella aerogenes* in two.

Radiographic findings

Ultrasonography delineated worms in four of the eight patients with pancreatic ascariasis and in 50 (91 per cent) of the 55 with biliary invasion (*Figure 1*); 36 had an enlarged poorly echogenic pancreas and three had a pseudocyst.

All patients underwent ERCP between 24 and 72 h after admission. Ascarides were seen to be moving actively in the duodenal lumen and invading the ampullary orifice in 44 patients. All those with severe pancreatitis had worms in the duodenum and blocking the ampullary orifice, but none of the four with pancreatic ascariasis alone had worms in the duodenum or invading the ampullary orifice. The bile duct was cannulated in all cases, and the pancreatic duct in 39. An attempt was made to fill the main pancreatic duct only. The pancreatic duct was dilated slightly (4–5 mm in the head) in patients with single-worm invasion of the pancreatic duct (*Figures 2* and *3*) but was found to be 9 mm in one patient with four-worm invasion. The pancreatic duct diameter ranged from 3 to 6 (mean 4·2) mm in the head region in patients with biliary tree invasion.

Treatment and follow-up

Initial treatment consisted of restricting oral intake and administration of intravenous fluids, antibiotics and analgesics. Effective anthelminthic therapy (mebendazole 100 mg orally twice daily for 3 days) was administered once the acute symptoms had subsided. In 33 patients with intractable pain not responding to analgesics, the worms from the duodenum and/or across the ampullary orifice were trapped during duodenoscopy with a polypectomy snare or a punch biopsy forceps and extracted via the mouth by withdrawing the endoscope along with the instrument holding the worms. Each of these patients had two to six worms extracted in one session and so sometimes needed repeated insertion of the endoscope; five with unremitting pain underwent two sessions of extraction. Endoscopic worm removal led to rapid relief of symptoms.

Eight patients with associated pyogenic cholangitis had a nasobiliary catheter (7-Fr ENBD catheter; William Cook, Bjæverskov, Denmark) placed in the bile duct at ERCP for biliary decompression and drainage. Worms were extracted from the bile duct in three of these eight patients by introducing a basket into the bile duct through the ampullary orifice at ERCP; the worms were then engaged and extracted from the bile duct. The endoscope was removed along with the basket

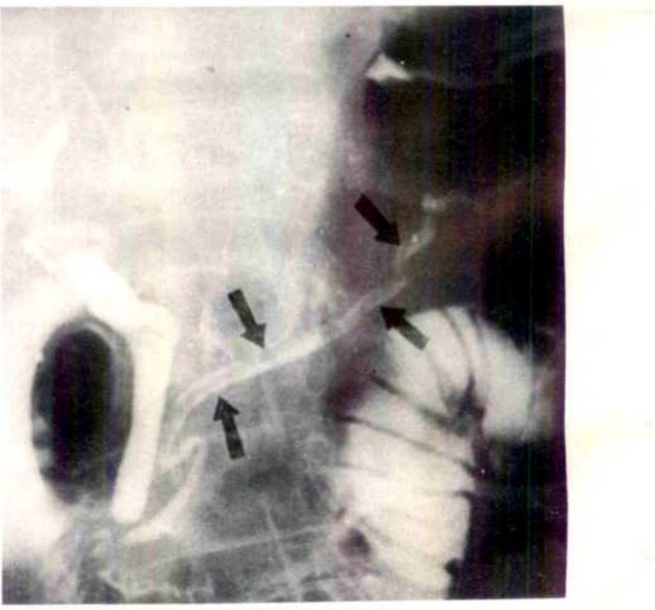

Figure 2 *Endoscopic retrograde cholangiopancreatography in a patient with mild pancreatitis revealing a long linear filling defect along the entire pancreatic duct (arrows)*

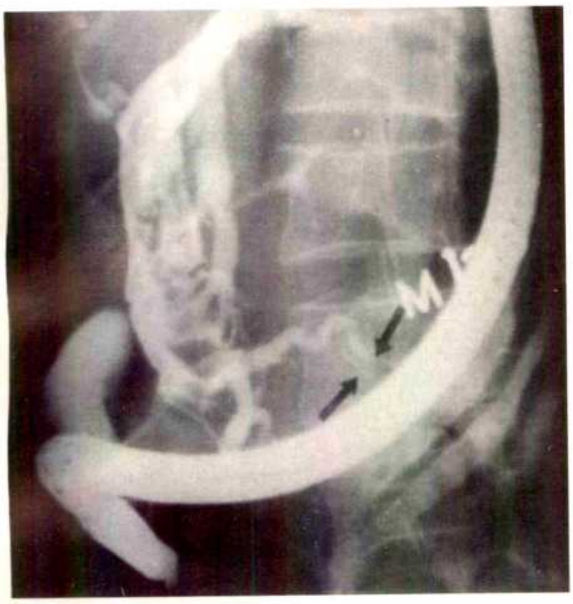

Figure 3 *Endoscopic retrograde cholangiopancreatography in a patient with severe pancreatitis. The pancreatic duct contains a linear filling defect in its distal half (arrows). The common bile duct is packed with multiple roundworms*

holding the worms. Endoscopic sphincterotomy was not performed in any of the present patients to facilitate extraction of worms.

A total of 56 patients (45 with mild pancreatitis and 11 of 13 with severe pancreatitis, including all eight with pyogenic cholangitis) recovered completely with a combination of conservative and endoscopic treatment and were discharged within 7–29 (mean(s.d.) 16(6)) days. The remaining three patients with intractable pain underwent surgery: one with haemorrhagic pancreatitis died following extraction of 15 worms from the biliary tree and four from the pancreatic duct; ten worms were extracted from the bile duct of the second through a choledochotomy; and surgery for an enlarging pseudocyst was performed in the third. The last two patients recovered.

In 53 patients, exit of worms from the ductal system was assessed by ERCP 6–8 weeks after the initial attack. Worms had moved out of the ducts in 47 and persisted in the biliary tree in six, in whom endoscopic extraction from the bile ducts was attempted. Endoscopic sphincterotomy was not performed to extract worms, which were successfully removed from the bile duct with the help of a Dormia basket in five cases. The single patient in whom endoscopic extraction failed has since undergone surgery, at which three dead worms were recovered from the bile duct. Patients were advised to take anthelminthic therapy every 2 months.

Of the 58 survivors, 36 had a mean(s.d.) follow-up of 19(7) (range 2–29) months. Thirteen episodes of severe abdominal pain requiring hospitalization occurred in ten patients, all of which (biliary colic in five cases, cholangitis in three, acalculous cholecystitis in two, pancreatitis in three) were caused by worm reinvasion of the biliary tree. No reinvasion of the pancreatic duct was noted. One patient with severe pancreatitis died on the seventh day in hospital during a second admission. All the others recovered rapidly with conservative treatment or extraction of worms from the papillary orifice (five cases). Five patients underwent ERCP during a symptom-free period to assess 'silent' worm reinvasion; none was present. None of the patients developed symptoms of pancreatic insufficiency or calcification.

Discussion

The aetiology of acute pancreatitis varies geographically. The present study shows ascariasis as an aetiological cause of this condition in 23 per cent of patients. Ascariasis has a worldwide distribution affecting one-quarter of the total population, mostly in developing countries in the tropics and subtropics[11]. Although ascariasis is rare in the developed world, clinicians should be aware of abdominal complications related to it because of the increased movement of tourists, immigrants and refugees[12–14].

Adult roundworms cause acute pancreatitis under the following circumstances: invasion into the bile duct through the papilla of Vater causing its blockage or spasm (biliary ascariasis); invasion into the pancreatic duct (pancreatic ascariasis); or both (biliary and pancreatic ascariasis). Invasion of the pancreatic duct is rare owing to its narrowness: in a series of 500 patients with hepatobiliary and pancreatic ascariasis, only seven (1·4 per cent) showed worms invading the pancreatic duct[10]. In the present study pancreatic ascariasis alone produced mild pancreatitis; partial blockage of the duct of Wirsung and a patent Santorini's duct may have protected these patients from developing a severe attack. Also, blockage of ampullary orifices may be critical in causing hypertension in the pancreatic duct and inducing severe pancreatitis. The ampullary orifice was not blocked by worms in any of the four patients with pancreatic ascariasis. In contrast, invasion of the biliary tract produced a more severe form of pancreatitis, with high morbidity. Because the adult worm has invaded the ampullary orifice, biliary obstruction usually presents with concurrent pancreatic obstruction. Simultaneous invasion of both the bile and pancreatic ducts led to severe pancreatitis in a high percentage of the patients studied. Both these situations probably caused pancreatic duct obstruction with bile regurgitation and entry of micro-organisms. These mechanisms both result in activation of pancreatic enzymes, with the development of pancreatitis.

Ultrasonography is a safe and reliable tool for delineating worms in the biliary tree and also for monitoring their exit[8,15,16]. However, its sensitivity for the detection of a single worm in the bile duct is only 50 per cent[8]. Ultrasonography also has only a limited role in the diagnosis of pancreatic ascariasis, due to its high false-negative rate[4].

ERCP is not only an excellent tool for detecting worms but it can also play a major therapeutic role in the management of ascariasis-related pancreatitis[3,14]. No complications were attributable to ERCP in the present series. Endoscopic extraction of worms from the duodenum and across the ampullary orifice led to rapid relief of symptoms. Removal of worms invading the ampulla of Vater facilitated drainage of the pancreatic duct and so favourably influenced the outcome. The actively moving ascarides in the duodenal lumen may invade the ampullary orifice to exacerbate pancreatitis, and their extraction via the mouth may also have contributed to the rapid recovery. Although only a randomized controlled trial can demonstrate the effect of this therapeutic procedure on morbidity, length of hospital stay and mortality rate, the rapid relief of symptoms in the present patients is impressive. Pancreatic pain not amenable to analgesics has become a major indication for urgent ERCP at this centre.

Biliary or pancreatic symptoms recurred in many patients due to worm reinvasion. Regular anthelminthic therapy every 2 months is necessary to ensure a worm-free intestinal tract in an endemic area where reinfection rates are so high. Worms were not seen inside the pancreatobiliary tree during the symptom-free period, an observation confirmed in a sonographic study of the prevalence of biliary tract worms in the general population[7].

In summary, this study has shown that ERCP and the endoscopic extraction of worms are safe procedures in patients with *Ascaris*-induced acute pancreatitis; a skilled endoscopist is required. Endoscopic removal of worms from the duodenum and ampulla of Vater favourably affect the outcome and serve as an effective alternative to surgery. This therapeutic procedure should be considered an important part of the overall management of such patients[17].

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Endoscopic management of postoperative bile leaks

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Thirty-two patients aged 15–89 years developed postoperative bile leakage. Twenty-eight had undergone cholecystectomy, with choledocholithotomy in 11, and four had had miscellaneous operations. Endoscopic retrograde cholangiopancreatography (ERCP) was performed 2–75 days after operation and revealed leakage from the cystic duct stump in 19 cases, from a T tube track in five, from the gallbladder and liver abscess cavity in two and from the major bile ducts in six. Major bile duct lesions were not generally amenable to endoscopic treatment, but the remaining 26 patients were treated successfully with internal stenting (22) or endoscopic sphincterotomy (four); bile secretion in all cases stopped within 1 week. One patient with cholangitis after an ERCP procedure was managed by antibiotics; no other complication occurred and there were no deaths related to the procedure. ERCP procedures are well tolerated in the postoperative period and may be performed under sedation. ERCP is the method of choice for dealing with bile leakage and ERCP procedures are effective for the most common causes of postoperative bile leakage; complications are rare.

Bile leakage is a rare but serious complication that may occur after biliary tract surgery. Usually the leak is from the cystic duct stump or common bile duct (CBD). Although cystic duct stump leakage often heals spontaneously, leakage from any site may cause accumulation of large quantities of bile in the peritoneal cavity, a potential hazard to the patient. Previously it was necessary to treat the leak surgically, with external drainage of any bile collection[1,2], but reoperation involves certain risks. In recent years, promising non-operative alternatives have been introduced into clinical practice[3–7]. This paper reports results with endoscopic treatment of patients with postoperative bile leakage.

Patients and methods

The case records of patients with iatrogenic biliary leakage in the period 1981–1989 were reviewed. There were 32 patients, 15 male and 17 female, with a median age of 54 (range 15–89) years. The primary operation was cholecystectomy in 17, cholecystectomy and choledocholithotomy in 11, and miscellaneous procedures in four (*Table 1*). Indications for postoperative endoscopic retrograde cholangiopancreatography (ERCP) were production of several hundred millilitres of bile through a drain in the early postoperative period, clinical signs of cholascos, or persistent bile secretion through a drain or cutaneous fistula. ERCP was performed at a median of 17 (range 2–75) days after the primary operation. Eight patients underwent reoperation before ERCP was performed: six for biloma or biliary peritonitis, one for retained common duct stones (twice) and one for persistent bleeding (twice).

ERCP was performed under sedation, with the patient in the oblique left lateral position, using Olympus duodenoscopes types JFB3, JF1T or JF1T10 (Olympus, Tokyo, Japan). If stenting was performed, a 7-Fr polytetrafluoroethylene double-pigtail catheter was used. ERCP showed leakage from the cystic duct stump in 19 patients, from a T tube track in five, from the gallbladder or a liver abscess cavity in two, and from major bile ducts in six (*Table 2*). One patient with leakage after simple cholecystectomy had been reoperated on because of cholascos, and a T tube was placed in the CBD. When the T tube was removed the patient developed severe bile secretion. Seven patients had

Table 2 *Sites of bile leakage and nature of treatment in 32 patients*

		Treatment		
Leakage site	No.	Internal stent	ES	CBD stones
Cystic duct stump	19	17	2	4†
T tube track	5	4	1	3†
Gallbladder	1	1	0	0
Liver abscess cavity	1	0	1	0
Major ducts	6	2*	1	0

ES, endoscopic sphincterotomy; CBD, common bile duct. * Nasobiliary catheter in one case; † stones removed endoscopically

Table 1 *Primary operation and site of bile leakage in 32 patients*

		Leakage site			
Operation	No.	Cystic duct stump	T tube track	Gallbladder or liver cavity	Major ducts
Cholecystectomy	17	14	1	0	2
Cholecystectomy and choledocholithotomy	11	5	4	0	2
Hepatic lobe resection	1	0	0	0	1
Liver abscess surgery	1	0	0	1	0
Gallbladder abscess surgery	1	0	0	1	0
Surgery for traumatic bleeding	1	0	0	0	1

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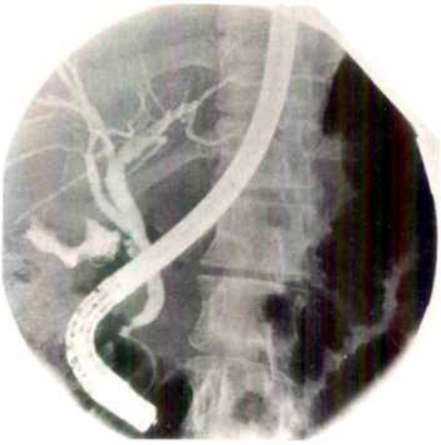

Figure 1 *Endoscopic retrograde cholangiopancreatography 5 days after operation showing cystic duct stump leakage in a 33-year-old woman who developed signs of cholascos after cholecystectomy*

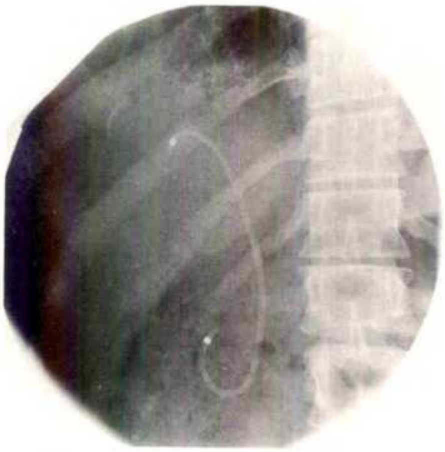

Figure 2 *Endoscopic retrograde cholangiopancreatography in the patient shown in* Figure 1 *after insertion of an internal stent*

retained stones in the CBD (*Table 2*), four with leakage from the cystic duct stump and three from a T tube track.

All retained stones were removed endoscopically. Cystic duct stump leakage (*Figure 1*) was treated with internal stenting in 17 instances (*Figure 2*) and with endoscopic sphincterotomy (ES) in two. T tube track leakage was treated with internal stenting in four instances and ES in one; leakage from the gallbladder was treated with internal stenting and from a liver cavity with ES. Major duct leakage in the patient after liver resection was caused by erosion of a suture line by a drain, which was, accordingly, withdrawn. Three CBD lesions were palliated with internal stenting, nasobiliary catheterization or ES, whereas no endoscopic treatment was possible in two patients with major duct lesions. When stenting was performed in patients without retained stones in the CBD, sphincterotomy was not performed. Additionally, five patients (four with cystic duct stump and one with T tube track leakage) were treated by ultrasonographically guided drainage of subhepatic or subphrenic biloma or abscess.

Results

Bile secretion through a drain or cutaneous fistula decreased immediately after treatment in all 27 patients with leakage from the cystic duct stump, T tube track, gallbladder, liver cavity or suture line of the liver resection and had stopped within 1 week. In all 22 patients undergoing internal biliary stenting, healing of leakage was revealed by ERCP when the stent was removed 1–3 months later. Two of the patients had an additional operation performed, one immediately after endoscopy to obtain sufficient drainage of cholascos and one 4 weeks after endoscopy because of a subhepatic abscess that was intractable to drainage by ultrasonographic methods. Five of the patients with major duct lesions underwent reconstructive surgery; it is doubtful whether the endoscopic procedure had any effect other than mapping anatomical structures.

One patient developed mild cholangitis after internal stenting and was managed by antibiotics. No bleeding or stricture occurred after stenting or ES. Four patients died. This could not, however, be ascribed to the endoscopic procedure in any instance, but was the result of age and general postoperative complications.

Discussion

Bile leakage after biliary tract surgery may present through a cutaneous fistula or drain without affecting the patient's general condition, or it may present with severe abdominal symptoms requiring acute intervention. Surgery in such conditions carries certain risks; often the source of the bile leak is unknown and may be difficult to define in an inflamed area.

ERCP has the potential for mapping the precise anatomy of the biliary tract and at the same time allowing a therapeutic procedure. General anaesthesia is not needed and the procedure can be performed under mild sedation within 30 min in most cases. Stress to the patient is, therefore, minimal. The present results demonstrate that the method is excellent for treating the most common sources of bile leakage after biliary tract surgery. All retained stones in the CBD could be removed and bile secretion stopped soon after either internal stenting or ES, indicating a quick healing of the fistula. The complication rate was very low. We prefer internal stenting to ES when there is leakage from the biliary ducts, both to be sure that the region of the sphincter of Oddi is effectively bypassed and to preserve the sphincter of Oddi itself, although it is necessary to perform a second endoscopic procedure to remove the drain. However, ES is probably equally effective because the resistance of the sphincter of Oddi is eliminated. Equally good results have been obtained in two other series[3,5]. The authors of these reports have used ES in cystic duct stump leakage and reserved internal stenting as a prophylactic measure for patients with signs of stricture distal to the leakage. They believe a long-standing stent carries certain risks in itself, especially of cholangitis. In the present series there was one case of cholangitis, managed by antibiotics.

In a recent report a nasobiliary catheter was recommended instead of an internal stent in the treatment of cystic duct stump leakage[8]. This enables cholangiography to be performed to establish closure of the leakage and eliminates the need for a second endoscopic procedure. On the other hand, nasobiliary catheters are not able to transport more than about one-third of daily bile production, even when suction is applied[6], because they are long and thin and transport is partly against gravity, unlike in an internal stent. They may, therefore, not be as effective as an internal stent; furthermore, they are much more uncomfortable for the patient. The single patient in the present series so treated suffered great discomfort.

Another non-surgical method of treating bile leakage is by percutaneous transhepatic drainage[4,7], which also seems to be effective in experienced hands. Retained stones in the CBD are a frequent cause of leakage[3] and it is more difficult to remove calculi by such a method. Also, the bile ducts are usually of normal calibre when there is leakage, which makes the procedure difficult. ERCP-related procedures are probably more widespread in clinical practice today and should, therefore, be the method of choice.

Generally, intraperitoneal bile collections are treated by surgical drainage[4,7] and several patients in this series were operated on for that reason, especially before endoscopic procedures were performed. Recent data strongly suggest that surgery should be replaced by percutaneous drainage guided by ultrasonography[9,10], making treatment much more convenient for the patient. A prerequisite is probably that ERCP is performed as soon as bile leakage is suspected, so that it is treated at once, minimizing the risks of bile collection and abscess formation. Major lesions cannot be treated endoscopically, but a diagnostic procedure is relevant to define the nature and site of the lesion.

In conclusion, ERCP is the method of choice in suspected postoperative bile leakage. Endoscopic treatment is very effective for the most common types of bile leak and carries a low complication rate. Together with ultrasonography it will probably replace surgery as the treatment for most bile leaks in the future.

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Role of endoscopic retrograde cholangiopancreatography in the investigation of pain after cholecystectomy

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Patients who continue to have or who develop abdominal pain after apparently successful cholecystectomy pose diagnostic difficulties. This study reports 384 such patients, investigated by endoscopic retrograde cholangiopancreatography (ERCP). There were 146 patients with abdominal pain alone with no previous history of common bile duct (CBD) exploration, of whom only 17 (11·6 per cent) had CBD stones on ERCP. Bile duct calculi were present in 76 of 140 patients (54·3 per cent) with abnormal biochemical findings (raised alkaline phosphatase and/or amylase level) and in 34 of 57 (60 per cent) with an abnormality detected on ultrasonography or intravenous cholangiography. A combination of biochemical and radiological abnormalities was present in 37 patients and was associated with CBD stones in 28 (76 per cent). Patients who had undergone CBD exploration represented a special group, of whom the majority (75 per cent) had common duct stones at ERCP even in the absence of biochemical and radiological abnormalities. ERCP is a useful investigation in patients with persistent postcholecystectomy symptoms. Other features in addition to pain or a history of CBD exploration may be relevant to the decision to perform ERCP in the investigation of these patients.

Despite careful selection and attention to operative detail, some patients continue to complain of abdominal pain following cholecystectomy In addition, patients may present later with abdominal pain after an initially successful operation While there are a number of possible reasons for this pain, a major cause is that of common bile duct (CBD) stones either missed at the original operation or recurring subsequent to it[1,2]. Until the advent of endoscopic retrograde cholangiopancreatography (ERCP) the diagnosis of such stones was difficult and their management problematic. ERCP has provided an accurate and satisfactory method for diagnosing CBD calculi and, with the development of endoscopic sphincterotomy (ES), offers the possibility of treatment during the same examination[1,2]

ERCP is, however, an invasive procedure and is associated with a small but significant risk of complications, particularly if ES is performed. Under these circumstances major complication rates of 8–10 per cent and mortality rates of 1–2 per cent have been reported[3–6] It is therefore desirable to restrict its use to those patients in whom there is a reasonable probability that CBD stones are present ERCP may be valuable in patients with abdominal pain after cholecystectomy[1,2,7] but it has to date proven difficult to define those in whom the procedure is most likely to be of benefit. This retrospective study aimed to define the factors that would predict the presence of CBD stones in patients referred for ERCP for persistent pain after cholecystectomy.

Patients and methods

The records were reviewed of all ERCP examinations performed within the Newcastle Health Authority region between 1 January 1976 and 31 December 1989 During this period over 5000 ERCP investigations were carried out These included 466 consecutive patients investigated for abdominal pain after a previous cholecystectomy (*Table 1*)

All ERCP investigations were performed by, or in the presence of, an experienced endoscopist (M I L , R L. or C.W.V) using an Olympus (JFB2, JFB1T, Olympus, Lake Success, New York, USA) or Fujinon (XL, Pyser, Kent, UK) duodenoscope. An attempt was made to visualize the pancreatic and biliary systems in every case and incomplete visualization of either duct was regarded as failed examination of that system

Features examined

The medical records for all of these patients were examined and the age, sex and time interval after cholecystectomy recorded It was noted whether or not the bile duct had been explored at the original operation. The clinical history was reviewed and results were recorded of serum alkaline phosphatase and amylase levels, and of the assessment of the CBD by ultrasonography and intravenous cholangiography Ultrasonography was available only after 1978 and was performed on 368 patients Intravenous cholangiography was carried out on 107

Abdominal pain was considered to be an indication for ERCP if it was epigastric or right hypochondrial, suggesting biliary or pancreatic pathology

Table 1 *Details of 466 patients with pain after cholecystectomy investigated by endoscopic retrograde cholangiopancreatography*

Clinical status	No	Sex ratio (M F)	Mean age (years)	Mean interval since cholecystectomy (months)
Pain only	150	24 126	54 8	78 4
Pain and clinical or biochemical abnormality	140	49 91	63·1	76·8
Pain and imaging abnormality	57	14.43	54 4	91 0
Pain and both clinical or biochemical and imaging abnormalities	37	8.29	61 6	87 6
Failed investigation	82	30.52	58·2	82 5
Total	466	125 341	58 4	83 3

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A raised serum amylase concentration was defined as that >90 units l^{-1} (normal range 20–90 units l^{-1}) at the time of admission with abdominal pain. Amylase assays were performed on a Cobas Mira instrument (Roche, Welwyn Garden City, UK) at 37°C using a blocked-substrate procedure consisting of *p*-nitrophenylmaltoheptaoside in the presence of glucose Amylase activity was measured kinetically at 405 nm.

A raised level of serum alkaline phosphatase was defined as one >115 units l^{-1} (normal range 25–115 units l^{-1}) measured either during an admission with abdominal pain or at the time of admission for ERCP. Alkaline phosphatase assays were performed on an Olympus AU5000 analyser at 37°C using sodium *p*-nitrophenylphosphate in 2-amino-2-methyl-1-propanol buffer at pH 10·5.

Imaging abnormalities were also sought. Biliary dilatation was defined as a CBD diameter >7 mm on ultrasonography using either an Acuson 128 (Acuson, Mountain View, California, USA) or Hewlett Packard 77020A (Hewlett Packard, Andover, Massachusetts, USA) or >11 mm on intravenous cholangiography. Biliary dilatation or the demonstration of a calculus by imaging was defined as an abnormal investigation. All intravenous cholangiograms were reviewed by one of the authors (M.I L.); ultrasonography was performed by one of seven radiologists Reported imaging investigations commented on the presence or absence of calculi or duct dilatation as defined above It was not attempted to record CBD diameter in every case.

Analysis of patient groups

The patients studied were divided into four groups on the basis of their history and results of investigations. These were: (1) presentation with abdominal pain without history of jaundice or pancreatitis and with normal investigation findings; (2) pain and an additional history of jaundice or pancreatitis, and/or recorded high alkaline phosphatase or amylase levels but no imaging abnormality; (3) pain and an imaging abnormality alone; and (4) pain and abnormalities in the history and biochemical and imaging investigations

Statistical analysis

Abnormality or a history of CBD exploration was assessed to predict the presence of any abnormality at ERCP, particularly the finding of common duct stones This was performed by a comparison of proportions using the χ^2 test. The mean ages and intervals after cholecystectomy in patients with normal and abnormal ERCP results were compared using Student's *t* test and the Mann–Whitney *U* test respectively.

Results

Successful cannulation of both biliary and pancreatic duct systems was achieved at ERCP in 384 patients (82·4 per cent), whereas cannulation of the pancreatic duct alone occurred in 25 (5·4 per cent) and that of the CBD alone in 20 (4·3 per cent). Neither duct was cannulated in 37 patients (7·9 per cent). Only those in whom both duct systems were cannulated were included in the analysis, to avoid the possibility that an alternative cause for the pain might be attributable to the duct system that was not cannulated.

Table 2 shows the relationship between the clinical, laboratory and imaging findings and the presence of an abnormality on ERCP. The distribution of CBD stones was significantly different in the four patient groups ($\chi^2 = 39{\cdot}62$, 3 d.f., $P < 0{\cdot}001$). The chance of finding stones at ERCP was significantly increased if there were any clinical, biochemical or imaging abnormalities present in addition to a history of abdominal pain ($\chi^2 = 54{\cdot}30$ and 45·30 respectively, 1 d.f, $P < 0{\cdot}001$) There was no significant increase ($\chi^2 = 0{\cdot}40$, 1 d.f., $P > 0{\cdot}05$) in the predictive value for duct stones whether the abnormalities before ERCP were clinical, biochemical or imaging in nature. The presence of both a clinical or biochemical and an imaging abnormality added significantly to the chance of finding CBD stones at ERCP compared with a clinical or biochemical abnormality alone ($\chi^2 = 5{\cdot}07$, 1 d.f., $P < 0{\cdot}003$) but not when compared with an imaging abnormality alone ($\chi^2 = 2{\cdot}43$, 1 d.f., $P > 0{\cdot}1$). Abnormalities other than stones found at ERCP are shown in *Table 2*

Both clinical or biochemical ($\chi^2 = 51{\cdot}99$, 1 d.f., $P < 0{\cdot}001$) and imaging ($\chi^2 = 61{\cdot}99$, 1 d.f., $P < 0{\cdot}001$) abnormalities significantly increased the diagnostic yield of ERCP Patients with abnormal findings on ERCP were significantly older (mean(s.d.) age 55·8(14·8) *versus* 61·5(4·6) years; $t = 5{\cdot}17$, 382 d.f., $P < 0{\cdot}001$). There was, however, no difference in the

Table 3 *Incidence of common bile duct stones found on endoscopic retrograde cholangiopancreatography in relation to clinical features and history of previous bile duct exploration*

	Common bile duct exploration	
Clinical status	Performed	Not performed
Pain only ($n = 150$)	3 of 4 (75)	17 of 146 (11·6)
Pain and any abnormality* ($n = 234$)	28 of 48 (58)	110 of 186 (59·1)

Values in parentheses are percentages. *Clinical or biochemical and/or imaging abnormality

Table 2 *Abnormalities and common duct stones in 384 consecutive successful endoscopic retrograde cholangiopancreatography investigations for pain after cholecystectomy*

Clinical status	Abnormal ERCP	CBD stones	Other diagnoses	
Pain only ($n = 150$)	29 (19·3)	20 (13·3)	Stricture at cystic duct–CBD junction	5 (3·3)
			Chronic pancreatitis	2 (1·3)
			Ampullary stenosis	2 (1·3)
Pain and clinical or biochemical abnormality ($n = 140$)	91 (65·0)	76 (54·3)	Ampullary stenosis	5 (3·6)
			Pancreas divisum	4 (2·9)
			Chronic pancreatitis	3 (2·1)
			Ampullary carcinoma	1 (0·7)
			Bilioenteric fistula	1 (0·7)
			Pancreatic carcinoma	1 (0·7)
Pain and imaging abnormality ($n = 57$)	42 (74)	34 (60)	Pancreatic carcinoma	3 (5)
			Leak from cystic duct stump	2 (4)
			Pseudocyst	1 (2)
			Ampullary stenosis	1 (2)
			Chronic pancreatitis	1 (2)
Pain and both clinical or biochemical and imaging abnormalities ($n = 37$)	33 (89)	28 (76)	Chronic pancreatitis	2 (5)
			Cholangiocarcinoma	2 (5)
			Duodenal diverticulum compressing CBD	1 (3)
Total ($n = 384$)	195 (50·8)	158 (41·1)		

Values in parentheses are percentages. ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct median interval between cholecystectomy and presentation with abdominal pain when the groups with normal and abnormal ERCP were compared (median (range) 54·4 (3–408) *versus* 48 (1–432) months, $P > 0\cdot5$).

The relationship of bile duct stones to a history of previous exploration of the CBD is shown in *Table 3*. When common duct stones were confirmed a successful ES with subsequent clearance of the duct (confirmed by repeat ERCP at 6 weeks) was performed in 98 patients (62·0 per cent). In a further 44 (27·8 per cent), repeat endoscopic procedures were required before the duct was cleared and in 16 patients (10·1 per cent) surgical clearance of the duct was necessary

Discussion

Although the majority of patients with gallstone-related symptoms are cured[8–12] by cholecystectomy, 5–40 per cent of patients continue to have pain or develop recurrent symptoms[8]. These patients generate difficulties in management and may undergo exhaustive investigation, often without a satisfactory conclusion.

A specific 'postcholecystectomy syndrome' does not exist[9], and many of these patients have other pathologies to explain their symptoms, such as peptic ulceration, gastro-oesophageal reflux or irritable bowel syndrome. The possibility of biliary or pancreatic pathology, however, is a natural source of concern to the clinician and requires investigation in many cases.

The advent of ERCP has improved the assessment of such patients. This investigation also provides an opportunity for treatment at the same time if common duct stones are found. However, as the procedure carries a small but definite risk and is relatively expensive it is important to define any subgroups of patients in whom the diagnostic yield of ERCP is likely to be particularly high[7]. The diagnostic yield of ERCP in the postcholecystectomy patient with abdominal pain is higher in patients with jaundice and/or pancreatitis[1,2,7]. In earlier studies[1,7] of patients without jaundice and/or pancreatitis, the incidence of normal ERCP findings was 33 and 38 per cent.

In the present study, 80·7 per cent of patients without a biochemical or radiological abnormality had normal ERCP examinations. The discrepancy between these results and those of earlier studies may reflect the fact that the present patients without jaundice and/or pancreatitis had normal biochemical findings (in particular, a normal serum alkaline phosphatase level), suggesting that in the absence of overt jaundice or documented pancreatitis, a raised alkaline phosphatase concentration will predict an additional number of patients likely to benefit from early ERCP. Another factor that may make comparison of separate studies difficult is selection bias in referral of patients for ERCP. This is difficult to rule out in any study but in the present case would have occurred before referral. All patients referred to this unit for management were investigated as described above.

The present total diagnostic yield at ERCP of 50·8 per cent is significantly lower than that of 73 per cent reported earlier[2] This discrepancy probably arises because the higher figure is based on a report in which patients known to have retained common duct stones and a T tube *in situ* were included, whereas the present study included only patients in whom the presence of pathology was unknown before ERCP, and those with a T tube were excluded Another possible explanation for the relatively low diagnostic yield in the present series is the low incidence of dysfunction of the sphincter of Oddi. Although the incidence of CBD stones is similar (or even greater) than figures reported previously, the overall incidence of ampullary stenosis in the present study is only 2 per cent, compared with 9 per cent reported by Neoptolemos *et al.*[13] in a similar group of patients This discrepancy may be due in part to patient selection, and failure in the present study to perform biliary manometry, which may be of value in predicting the response to ES in these patients.

The presence of an imaging abnormality (usually biliary dilatation) was of predictive value for an abnormality at ERCP, although imaging alone was not a better predictor than the finding of a biochemical abnormality alone. The presence of both imaging and biochemical abnormalities was, however, of greater predictive value than biochemical abnormalities alone.

The role of an isolated imaging abnormality must be considered in the light of the well recognized biliary dilatation that follows cholecystectomy, even in patients without biliary symptoms[14]. Although this was taken into account by the radiologists reporting imaging investigations, the interpretation of such abnormalities has been questioned[15]. In the present study, bile duct diameter was simply classified as 'normal' or 'dilated'. A measurement of CBD diameter in relation to age might have allowed an assessment of whether a cut-off size would lead to refinements in the predictive value of imaging investigations.

It is difficult to explain why a history of previous CBD exploration is such a good predictor of an abnormality at ERCP, and in particular, common duct stones. Although the numbers involved are small relative to the group as a whole, it is a cause for concern that the majority of patients who have undergone previous common duct exploration and continue to complain of pain have biliary pathology. This suggests that these patients should always be investigated by ERCP

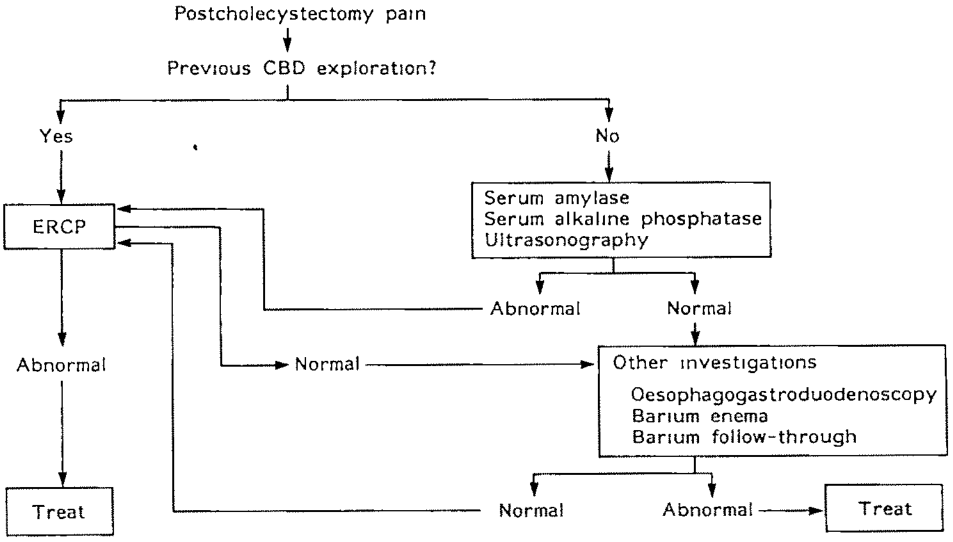

Figure 1 *Suggested management plan for patients with pain after cholecystectomy. ERCP, endoscopic retrograde cholangiopancreatography, CBD, common bile duct*

irrespective of the presence of another abnormality The majority of these patients have CBD stones Many of these calculi must have been left behind at the original exploration, although a proportion could have recurred within the duct system at a later time. There is increasing evidence, obtained from follow-up studies after clearance of the bile duct at operation and by ES, that bile duct calculi can re-form within the CBD, particularly when the duct is large in calibre[16]. This suggestion is supported by the long interval between a symptomatically successful operation and a new presentation with upper abdominal pain, leading to the diagnosis of stones in many of these patients.

In summary, ERCP is a valuable method of assessing patients likely to have biliary or pancreatic pathology after cholecystectomy. The absence of biochemical and/or imaging abnormalities at assessment before ERCP may enable a more rational and cost-effective approach to this difficult group of patients by selecting for other investigations those who are likely to have a normal ERCP finding (*Figure 1*).

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Common bile duct diameter and complications of endoscopic sphincterotomy

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To assess the relationship between distal common bile duct (CBD) diameter and the incidence of an immediate complication following endoscopic sphincterotomy (ES), all patients undergoing ES between January 1986 and October 1990 were studied. The overall risk of an immediate complication following ES in 655 patients was 5·6 per cent (37 patients). Patients with calculi were at greater risk if the distal CBD was dilated ($P < 0.001$*); the complication in those with stones was most likely to be haemorrhage (81 per cent). The relative risk of a complication increased ten times if the distal bile duct diameter was >0·8 cm. Patients with stricture of the distal CBD did not have a significantly greater risk of complication than those with stones (9·7* versus *4·9 per cent). There was no significant difference between the mean distal CBD diameter of those with stricture and controls (0·61* versus *0·44 cm).*

Endoscopic sphincterotomy (ES) is often required to remove common bile duct (CBD) stones and to treat bile duct obstruction due to neoplasm and stricture. In experienced hands, ES has a 30-day mortality rate of 0·5–1·5 per cent and morbidity rate of 2·5–11·3 per cent[1,2]. The complication rate decreases with greater experience[2–4] and increases with patient age[4,5] ES may be more hazardous in those with a relatively small papilla and a CBD that is either non-dilated or tapers distally[6]. In patients with dysfunction of the sphincter of Oddi, the risk of complication is greater in individuals with a small-diameter CBD[7]. In this study, the relationship between duct diameter and the incidence of haemorrhage and retroperitoneal perforation (complications directly related to ES) was examined.

Patients and methods

Between January 1986 and October 1990 a total of 655 patients, of median age 71 (range 22–95) years underwent ES. Of these, 552 (84 per cent) had ES for choledocholithiasis and 103 for malignant (96) or benign (seven) stricture

The length of sphincterotomy was tailored to the size of the stone or to achieve access to the bile duct. Although difficult to measure, the length of incision performed can be related to anatomical landmarks For small stones (<0·5 cm in size) in normal-calibre ducts, sphincterotomy was extended to the upper limit of the visible intramural segment of the CBD For stones between 0·5 and 1·5 cm in diameter, ES was extended on to the plane above the papilla, but short of the transverse fold For stones >1·5 cm, sphincterotomy was extended towards the transverse fold The diameters of the common hepatic duct and distal CBD were measured on the films, the latter at a constant point immediately above the choledochal sphincter (*Figure 1*) The diameter of the most distal calculus was measured in 25 of 27 patients who had stones and a complication Magnification was determined from the diameter of the endoscope It was impossible to measure stone size in two patients because of the position of the endoscope on the films Measurements were made in patients with complications and in paired patients without complication. They were matched by pathology and then by age, 86 per cent of the pairs being age-matched to within 4 years Control patients had a median age of 72 (range 30–89) years and patients with complications a median age of 71 (range 34–93) years

Haemorrhage was defined as a fall in haemoglobin concentration of ≥2 g/dl. Retroperitoneal perforation was diagnosed by detection of free gas on films taken routinely after the procedure[8].

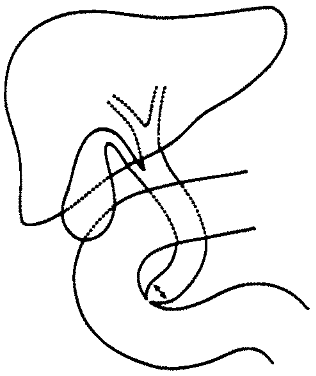

Figure 1 *Hepatobiliary system with arrows showing the point of measurement of the distal common bile duct immediately above the choledochal sphincter*

Results

Thirty-seven patients (5·6 per cent) had a complication during the procedure directly related to ES. Twenty-seven had duct stones, two had benign strictures and eight malignant obstruction of the distal bile duct. The complication rate in patients with stones was 4·9 per cent; it was 9·7 per cent in those with stricture. This difference was not statistically significant (Yates' $\chi^2 = 2.9$, 1 d.f., $P = 0.09$).

There was no death directly related to ES. Haemorrhage occurred in 28 patients (*Table 1*) and was the most common complication (81 per cent in patients with stones, 60 per cent in those with stricture, 76 per cent overall) Four patients needed transfusion and two required laparotomy to control haemorrhage. Retroperitoneal perforation occurred in nine patients (24 per cent); it was often clinically silent[8]. The diameter of the distal CBD in patients with complications had a geometric mean of 0·92 (range 0·3–2·8) cm In the control group, the geometric mean was 0·56 (range 0·2–1·2) cm. This difference was highly significant (paired $t = 5.2$, 36 d.f., $P < 0.001$). Patients with haemorrhage had significantly wider ducts than the control group (paired $t = 5.2$, 28 d.f., $P < 0.001$), those with perforation had a CBD diameter equal to the controls ($t = 1.8$, 7 d.f., $P = 0.11$).

Patients with stones and a complication (*Table 2*) had significantly wider distal ducts than the control group (paired $t = 6.3$, 26 d.f., $P < 0.001$) and patients with stricture and a

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Table 1 *Complications of endoscopic sphincterotomy*

	Haemorrhage	Retroperitoneal perforation
Stones	22	5
Malignant stricture	5	3
Benign stricture	1	1
Total	28	9

Table 2 *Distal common bile duct diameter after correction for magnification*

Group	No	Geometric mean (95% confidence interval) (cm)	P*
Controls	27	0·61 (0·55–0·66)	$<0·001$
Patients with stones	27	1·04 (0·90–1·21)	
Controls	10	0·44 (0·28–0·66)	0·23
Patients with stricture	10	0·61 (0·42–0·87)	

*Student's paired *t* test

complication (two-sample $t = 3·4$, 35 d.f., $P < 0·002$) There was a weak but significant correlation ($r = 0·6$, $P < 0·05$) between the size of the most distal stone and the diameter of the distal duct In three patients the obstructing calculus was wider than the distal CBD because of its more proximal impaction A degree of distal duct dilation was still present, however, at the point of measurement. There was no statistically significant difference between the duct diameter of the patients with a stricture and a complication and that of the control group (paired $t = 1·3$, 9 d.f., $P = 0·23$). The estimated relative risk (odds ratio) of a complication was ten times greater in patients with a distal duct diameter $>0·8$ cm than in those with a duct $\leqslant 0·8$ cm.

The type of complication was not significantly associated with the type of obstruction ($P = 0·17$, Fisher's exact test). The mean common hepatic duct diameter (0·13 (95 per cent confidence interval $-0·23$ to 0·49) cm) did not differ between those with complications and controls (paired $t = 0·7$, 36 d.f., $P = 0·47$).

Discussion

Risk factors related to complications after ES include experience of the endoscopist[2–4]; enlarging a pre-existing sphincterotomy[4]; age of the patient[4,5]; serum bilirubin and albumin levels[9]; and coagulation factors[10]. This study evaluated the relationship between bile duct diameter and the risk of developing an immediate complication of ES Sphincterotomy may be more hazardous in patients with a duct that is not dilated or tapered distally[6], particularly if performed for dysfunction of the sphincter of Oddi[7].

The overall complication rate was 5·6 per cent. Patients with stricture of the distal biliary tree did not have a significantly higher complication rate than those with stones (9·7 *versus* 4·9 per cent) Haemorrhage and retroperitoneal perforation were assessed as these were directly related to ES. Pancreatitis is not a direct complication of ES, but occurs because of manipulation of the papilla during the attempt to gain access to the CBD. It occurs if there have been repeated cannulations of the pancreatic duct Cholangitis may follow ES, but usually occurs because of failure to achieve adequate biliary drainage By following an active policy of clearing stones from the ducts immediately after ES, this risk of cholangitis is negated[11].

In patients with haemorrhage, the diameter of the distal CBD was significantly greater than in controls. Haemorrhage was the most common complication (81 per cent in patients with stones, 60 per cent in those with stricture, 76 per cent overall).

In about 4 per cent of patients, the gastroduodenal artery or a major branch of this vessel lies in the region of the sphincterotomy incision, and the length of the latter may therefore correlate with the risk of haemorrhage[3]. This study suggests that the degree of duct dilation is related to the size of the most distal stone. When the duct is dilated by a stone larger than the normal CBD diameter, the sphincterotomy required will be longer than in a normal-calibre duct, making vessels more vulnerable to damage. Previous studies indicate that depth of jaundice, results of clotting studies and liver function are not associated with a major risk of haemorrhage[2,4,8,10]. Other factors may influence mortality following a complication but do not affect the initial risk of developing the complication.

Perforation of the duodenum and bile duct usually occurs at the choledochoduodenal junction. In this study, distal duct diameter in patients who developed a perforation did not differ from that of paired controls.

Contrary to previous data[6], this study shows that patients who have dilated distal ducts due to stones are more likely to have a complication than those with a normal-calibre duct and calculi. The risk of a complication of ES is greater in narrow-calibre ducts in patients with dysfunction of the sphincter of Oddi[7]. The most common complication in this study was haemorrhage and this was related to the size of the calculus and the length of ES required. Haemorrhage was more likely to occur if the distal duct was dilated, irrespective of cause, CBD dilation may cause the local vessels to be more vulnerable. There was a tenfold increased risk of complication if the distal duct was $>0·8$ cm in diameter It may be prudent to reduce the size of the obstructing calculus by mechanical lithotripsy to reduce the length of ES required while allowing successful duct clearance

Acknowledgements

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Laparoscopic gastroenterostomy for malignant duodenal obstruction

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Surgical technique

An 82-year-old woman (patient 1) and a 78-year-old man (patient 2) presented with a history of several months of weight loss and vomiting Endoscopic and radiological investigations revealed an occluding adenocarcinoma in the third part of the duodenum with infiltration into the pancreas in patient 1 and extrinsic compression at the junction of the third and fourth part of the duodenum in patient 2 Neither had evidence of biliary obstruction.

Both patients underwent operation under general anaesthesia with a nasogastric tube *in situ* Peroperative antibiotic prophylaxis was given intravenously The patients were placed in a modified Lloyd-Davies position with a minor degree of reverse Trendelenburg tilt. The operator stood between the patient's legs with the assistant on the patient's right side A 10-mm laparoscope with endocamera attached was inserted through an umbilical cannula and general laparoscopy was performed, confirming advanced carcinoma in both patients Accessory subcostal ports were established as shown in *Figure 1* Using atraumatic graspers, the duodenojejunal flexure was identified and the forceps 'walked' down the jejunum for approximately 40 cm A suitable length of jejunum was then raised over the transverse colon and apposed to the inferior margin of the greater curvature of the stomach using two transabdominal stay sutures placed with the aid of an endoscopic needle holder While maintaining traction on the stays, the forks of an Endo-GIA stapler (US Surgical, Norwalk, Connecticut, USA) were inserted via the 12-mm cannula into enterotomies created by hook diathermy, closed and fired (*Figure 1*) In patient 1 a single firing of the 30-mm cartridge was used, in patient 2 two firings created a larger stoma The enterotomies were closed using a continuous 2/0 Nurolon (Ethicon, Edinburgh, UK) suture on a 30-mm needle mounted on a 5-mm endoscopic needle holder, a technique similar to that described by Shimi *et al* [1]

Results

Both operations were completed within 2 h. The nasogastric tube was removed the day after operation and oral fluids were introduced after 48 h Full diet was tolerated within 4 and 3 days. Postoperative pain was controlled by oral analgesia. Patients were discharged on the fifth and fourth days. At gastroscopy 6 weeks after operation, both stomas were patent and dependent. At this time both patients were able to eat a normal diet with complete relief from vomiting. Patient 2 died 16 weeks after operation from advanced metastatic disease

Discussion

The principal advantage of the laparoscopic approach is that it avoids an abdominal incision. Two firings of the 30-mm Endo-GIA are recommended, as this approximates more closely to the size of a linear stapled anastomosis at open operation[2] and is more likely to result in a dependent stoma. Although neither of the present patients had biliary obstruction, the procedure could be combined with endoscopic cholecystojejunostomy[1] to achieve complete palliation in patients with both duodenal and biliary obstruction. The laparoscopic approach removes the discomfort and debilitation of laparotomy for such patients, who by the nature of their disease would gain most from the resulting reduced hospitalization and minimal convalescence.

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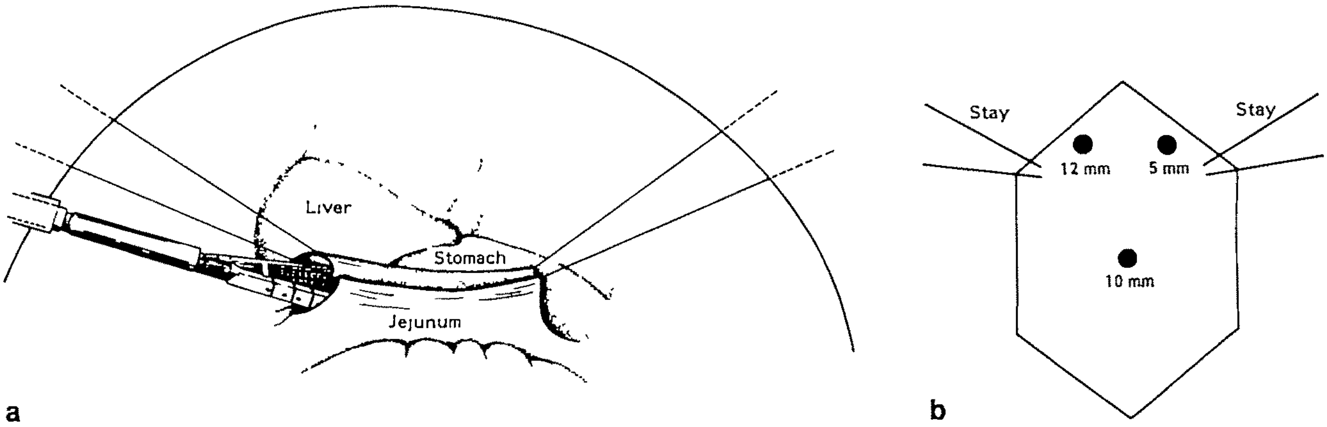

Figure 1 **a** *Transabdominal stay sutures and laparoscopic stapling technique* **b** *Relative positions of the ports and stays*

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Intrahepatic cholangiogastrostomy for malignant biliary obstruction at the hilum

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In 1948, Longmire and Sandford described a technique for draining the segment II duct of the liver when approach to the hilum was not possible[1]. With wider use of the ligamentum teres approach to the left duct and segment III duct, the Longmire operation is now restricted either to patients who have left lobe hypertrophy and consequent difficulty in subhepatic dissection of the main duct, or where the left duct is involved by malignant disease[2]. This technique is also useful where bulky disease in the subhepatic area from locally advanced bile duct malignancy prevents access to the main left hepatic duct or the segment III duct by the ligamentum teres approach.

This report describes a modification of the Longmire operation in which the stomach instead of the jejunum is used for drainage of the segment II duct of the liver.

Surgical technique

The left lobe of the liver is mobilized by division of the left triangular ligament. A clamp is applied to the left of the ligamentum teres (*Figure 1a*) The peripheral part of the liver is resected When the liver is bulky because of lobar hypertrophy, interlocking plastic strips are used in place of a clamp, to prevent parenchymal tears[3] A polythene cannula (usually 8–10 Fr) is inserted in the segment II duct Sutures are then placed over the cut edge of the liver for haemostasis The stump of the left lobe lies in close proximity to the anterior wall of the body of the stomach A posterior layer of interrupted 0 polyglactin 910 sutures is placed between the seromuscular layer of the anterior surface of the stomach, close to the lesser curvature, and the liver parenchyma and posterior capsule. An opening corresponding to the diameter of the segment II duct is made in the stomach (*Figure 1b*). Duct-to-mucosa anastomosis is performed using interrupted 3/0 polyglactin 910 sutures that incorporate the full thickness of the stomach wall and then pass from within the duct outwards, including surrounding parenchyma. Knots are tied on the outside. The anastomosis is completed around a transanastomotic polythene cannula with side holes along its entire length (*Figure 1c*) Finally, an anterior layer of 0 polyglactin 910 sutures is placed between the seromuscular layer of the stomach and the liver parenchyma and anterior capsule (*Figure 1d*) The cut surface of the liver is thus completely covered by gastric serosa.

Results

Intrahepatic cholangiogastrostomy was performed in seven of 31 patients with locally advanced bile duct carcinoma. Those with atrophy of the left lobe were excluded In all cases the left duct was patent on percutaneous transhepatic cholangiography but could not be approached by subhepatic dissection because of tumour in that area. Four patients had right lobe atrophy with hypertrophy of the left liver. Five had tumour extending down the hepatoduodenal ligament, causing duodenal obstruction, a gastrojejunostomy was performed in these There were no deaths.

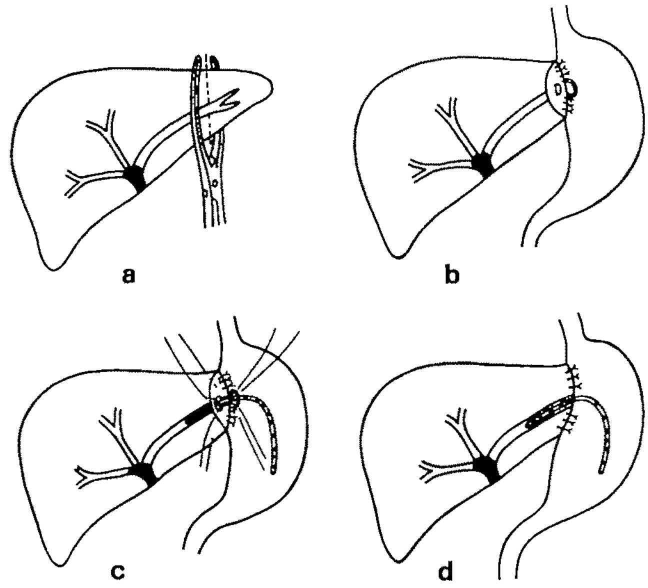

Figure 1 *Steps in the technique of intrahepatic cholangiogastrostomy*

All patients had prompt relief of jaundice. Serum bilirubin levels decreased from a mean of 414 (range 171–599) mmol/l to half of this by the fifth day after operation, and to normal within 25 days of discharge from hospital. Upper gastrointestinal forward-viewing endoscopy 6 weeks after operation showed a functioning patent anastomosis in all cases There were no clinical or endoscopic findings suggestive of bile gastritis Patients lived for a mean of 166 (range 78–282) days and remained anicteric till death.

Discussion

Cholangiogastrostomy has several advantages over cholangiojejunostomy· anastomosis between the stomach and the stump of the left liver is technically easy, as the organs are fixed in juxtaposition, the thick stomach wall provides a better buttress against leakage, the presence of bile in the nasogastric aspirate is a reassuring sign that confirms anastomotic patency, and operating time is reduced Two patients in the present series had retroperitoneal lymph node enlargement extending into the small bowel mesentery, resulting in considerable thickening and foreshortening of the mesentery so that construction of a Roux-en-Y limb would have been technically difficult

Cholangiogastrostomy does, however, have potential disadvantages anastomotic leakage would be of combined bile and gastric juice, whereas the leakage is predominantly of bile following drainage to the jejunum. Bile gastritis never occurred in any of the patients described in this paper There is also a tendency for sutures to cut through the liver parenchyma, although this is common to both operations. It can be prevented by including a considerable thickness of liver parenchyma in the suture and by not tightening the latter excessively.

In conclusion, intrahepatic cholangiogastrostomy is technically easy and safe for palliation in selected patients with hilar obstruction where a subhepatic approach is not possible, and appears to have advantages over Roux-en-Y cholangiojejunostomy. The best results are achieved in patients with hypertrophy of the left liver.

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Clinical evaluation of the LaparoLith intraoperative lithotriptor

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One of the outstanding problems in laparoscopic cholecystectomy is extraction of the gallbladder in the presence of a large stone load[1] This may delay the procedure and often necessitates either mechanical crushing and piecemeal removal using Randall's forceps or enlargement of the abdominal incision. Ultrasonic lithotripsy is practised by some[2] to reduce the stone burden and facilitate delivery of the gallbladder through the parietes, but the technique is time consuming. Mechanical dilators are available that shield the gallbladder while enlarging the exit wound, but their use is accompanied by loss of pneumoperitoneum, which more often than not results in blind extraction of the organ. This problem has led to the development of an efficient rotary mechanical lithotriptor which, after extensive bench-top and experimental testing[3], was submitted to clinical evaluation.

Surgical technique

The LaparoLith lithotriptor (EndoMedix, Irvine, California, USA) is an electromechanical device that rotates a metal impeller inside a fixed protective cage. When activated inside a dissected partially exteriorized gallbladder, the rotating impeller creates a fluid vortex that lifts the gallstones into contact with the revolving blades, resulting in rapid stone fragmentation. The unit consists of a drive system (motor controller, motor handpiece, drive train and accessories) and a disposable lithotriptor kit (introducer, rotor and infusion–aspiration syringe)

Initial evaluation was performed on eight patients with multiple gallstones after exteriorization of the gallbladder neck Lithotripsy was successful in four (mean stone size 19 0 (range 5 0–35 0) mm). Problems were encountered with the introducer, the plastic cage of which became damaged during insertion in two patients and caused mucosal dissection of the gallbladder without perforation in a third The device was not used in one patient because of motor failure. These preliminary results led to modification of the introducer system, the most important being the incorporation of an obturator The components of the final device are shown in *Figure 1*.

Clinical evaluation was conducted in accordance with a set protocol adopted by the participating centres Following exteriorization of the neck of the gallbladder and isolation of the wound with swabs, an incision is made that is large enough to accommodate the introducer just distal to the cystic duct clip. The introducer with obturator *in situ* is then guided inside the gallbladder until the tip is seen impinging on the fundus It is then withdrawn 1–2 cm and the gallbladder clamp applied across the neck flush with the skin (*Figure 1*). The obturator is removed and a 50-ml syringe containing isotonic saline attached to the infusion port The gallbladder is filled with saline and aspirated repeatedly until the escaping fluid is clear, so as to remove debris, agitate and disengage the stones and flush out air Once this is achieved, the shutter valve is closed and saline injected until the gallbladder is fully distended

The tip of the fully assembled handpiece (with drive train and rotor) is then inserted inside the introducer until it clicks into place This opens the cage within the gallbladder. The introducer is then gently withdrawn while the gallbladder is held stationary, until the dome of the expanded protective cage abuts on to the abdominal wall At this stage some air will still be present at the apex of the intra-abdominal gallbladder and should be flushed out by further injection of saline while the external gallbladder clamp is momentarily released.

Efficient lithotripsy is achieved by short repeated bursts (5–10 s), with brief pauses (2–3 s) between each. Successful fragmentation is detected by a grating sensation and gentle oscillation of the gallbladder. The absence of an initial grating sensation signifies that the stones are not being engaged by the impeller and that fragmentation is not

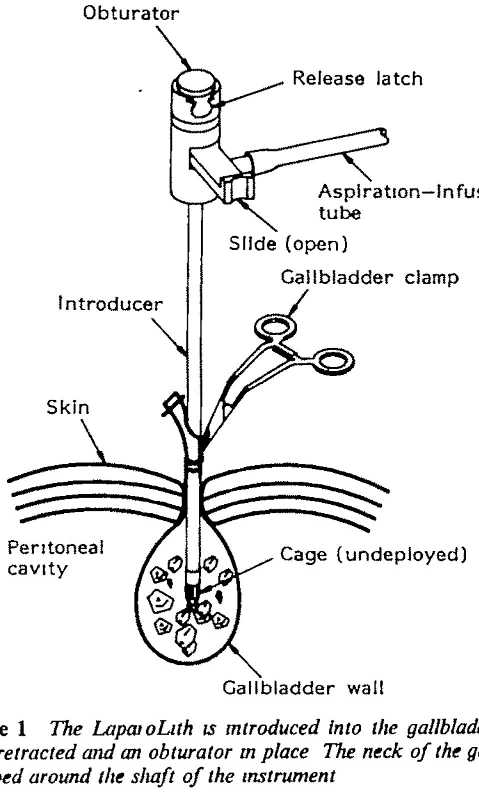

Figure 1 *The LaparoLith is introduced into the gallbladder with the cage retracted and an obturator in place The neck of the gallbladder is clamped around the shaft of the instrument*

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occurring. Cessation of the grating sensation following several bursts of rotation indicates that fragmentation is complete

After completion of lithotripsy, the handpiece is withdrawn and the shutter valve closed. The tip of the introducer is then pushed down to the fundus and the gallbladder contents aspirated. Infusion of saline is needed to dilute and suspend the resulting 'biliary sand' that tends to accumulate at the bottom of the gallbladder. The process is repeated until the gallbladder wall collapses over the introducer, at which stage both are removed through the abdominal wall by gentle traction.

The device was defined as 'not used' if the introducer was not inserted into the gallbladder. 'Successful' lithotripsy was defined as fragmentation within 3 min and gallbladder extraction through a 1·0-cm wound. 'Unsuccessful' lithotripsy occurred when the introducer was inserted but adequate fragmentation was not achieved within 3 min and other methods were used to extract or fragment stones and deliver the gallbladder.

Comparisons between groups were made with the Mann–Whitney U test. Correlations between rotation time and stone number or size in patients undergoing successful lithotripsy were assessed by linear regression analysis using the linear model ($y = a + bx$).

Results

The evaluation was performed on 72 patients (17 men, 55 women) undergoing laparoscopic cholecystectomy for symptomatic gallstone disease. The median age was 54 (range 20–86) years.

The LaparoLith was not used in 27 patients (38 per cent) because of small stone load ($n = 16$), perforated gallbladder ($n = 3$), fibrosed gallbladder ($n = 4$), device malfunction ($n = 2$) and other reasons ($n = 2$). Successful lithotripsy with extraction of the gallbladder through the 1·0-cm incision was achieved in 38 of the 45 remaining patients (84 per cent) Calculation of the exact stone burden was not possible as the size of only the largest stone was available. There was no correlation between rotation time and number of stones (median 6 (range 1–50); $r = 0{\cdot}39$) or between maximum stone size (median 11 (range 3–35) mm) and rotation time ($r = 0{\cdot}09$) in this group.

Failed fragmentation was observed in seven patients, including two with motor or device malfunction (*Table 1*). The most frequent cause for an unsatisfactory outcome was a large stone impacted in the fundus. Although the number of gallstones did not differ from that of the successfully treated group, the maximum stone size was significantly higher in the group in whom lithotripsy failed ($P = 0{\cdot}0007$).

Device malfunction during attempted use was encountered in four cases (9 per cent) and led to failed extraction in two.

Table 1 *Details of failed lithotripsy in seven patients*

Operative finding	
No of gallstones*	5 5 (1–25)
Largest stone size (mm)*	30 (15–37)
Fibrotic non-distensible gallbladder	1
Impacted large stones	4
Surgical perforation	1
Motor or device malfunction	2

*Values are median (range)

Discussion

One of the difficulties encountered at laparoscopic cholecystectomy is delivery of a gallbladder containing a large stone load Forceful extraction may result in rupture of the gallbladder with contamination of the wound and peritoneal cavity and the risk of retained stones within the latter. In two large multicentre series, superficial infection at the site of gallbladder extraction was the most common postoperative complication[1,4]. The risk of wound contamination and gallbladder perforation is increased by prolonged manual extraction and crushing of the stones by a Randall's or Desjardin's forceps. Extension of the incision does facilitate removal but may result in greater wound pain and hernia formation.

The present clinical evaluation has demonstrated that extraction of the gallbladder is facilitated by the use of the LaparoLith lithotriptor in over half of the patients submitted to laparoscopic cholecystectomy. The efficacy of this rotary electromechanical device in patients with a large stone load was 84 per cent. The need for its use in the individual patient may be determined from preoperative ultrasonography This study has identified the reasons for failure of disintegration by this technique. As the method relies on the creation of a fluid vortex to bring the stones into contact with the rotating impeller, the system functions only if there is sufficient gallbladder fluid volume for an effective vortex to be created. It is also dependent on the calculi being loose or capable of disengagement so that they can be lifted by the vortex to the impeller. Fragmentation is thus not achieved if the gallbladder is contracted or if the stones are large and impacted. These problems are inherent to the system as described and their documentation by the present trial has led to preliminary studies on the use of a tissue retrieval system This subsequent experience has confirmed that transfer of the gallbladder to a tissue retrieval bag, followed by extraction of the emptied viscus and lithotripsy inside the bag, can overcome these problems.

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Liver trauma: a 10-year experience

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The management of 73 patients with liver trauma (58 male, 15 female; mean age 30 (range 6–68) years) presenting from January 1980 to August 1990 is reviewed. There were 29 cases of penetrating injury and 44 of blunt trauma. Seven patients were successfully managed without operation (five with blunt injury) and were discharged after a mean hospital stay of 8 days. Fifty-one cases were classified as simple injuries (grade I or II) and were managed by suture (with or without drainage) or required no intervention, with three deaths. Fifteen cases were classified as complex injuries (grade III or IV) and underwent one or more of the following: perihepatic packing, resectional debridement, hemihepatectomy and hepatotomy with direct suture ligation. Six of these patients died from uncontrolled haemorrhage. The continued use of suture for simple injuries and of resectional debridement and/or packing for complex injuries is supported. Judicious clinical assessment and radiological monitoring may reduce the number of unnecessary laparotomies.

The liver is commonly injured in abdominal trauma. The severity of liver injury varies widely; the majority of wounds are minor and many of these do not require surgical intervention. Major liver injuries, often in association with multiple organ trauma, are difficult to manage and associated with high morbidity and mortality rates. Severe hepatic trauma continues to present a challenging problem and several aspects of management remain controversial. This type of injury is relatively uncommon in civilian practice in the UK and most surgeons consequently have only a limited experience. This study describes the 10-year experience with liver trauma presenting to general surgical units at a large teaching hospital that now provides a regional trauma service.

Patients and methods

The case notes of 73 consecutive patients who presented with liver injuries to this hospital from January 1980 to August 1990 were reviewed. Cases were identified from the computer records of the Lothian Health Board SMR 1 discharge data file and the Lothian Surgical Audit.

Two groups of patients were defined: one treated conservatively in that they were not submitted to laparotomy within 12 h of admission, the other managed by operative intervention. The severity of liver injury in those undergoing surgery was graded I–IV according to the classification of Calne *et al* [1] (*Table 1*). Patients were further classified according to the type of management. Those with injuries of grade I or II could be dealt with by simple surgical techniques such as careful appositional 'liver suture', the application of topical haemostatic agents and/or perihepatic drainage, and were regarded as having had simple injuries. Grade III or IV injury required more complex surgical procedures such as hepatic resection or debridement, perihepatic packing with delayed pack removal, and hepatotomy with selective vascular ligation. Such patients were classified as having complex injuries. An Injury Severity Score (ISS)[2] was assigned and those with isolated organ injuries identified. Shock was defined as systolic blood pressure <100 mmHg on admission. The series included no patient with liver injuries who died during initial resuscitation without operative intervention.

When intra-abdominal injury was suspected following blunt trauma, diagnostic peritoneal lavage was performed using an 'open' technique through a small lower midline incision. Lavage was deemed positive when the effluent consisted of frank blood or was heavily bloodstained; laboratory criteria such as red cell count were not used for interpretation. Those patients with evidence of haemoperitoneum and/or shock were immediately taken to the operating theatre and laparotomy carried out.

In patients with penetrating trauma, exploratory laparotomy was undertaken if the patient was shocked, had signs of peritoneal irritation or evisceration, and when peritoneal penetration was suspected. There was no selective policy for conservative management in these patients and local wound exploration and diagnostic peritoneal lavage were not routinely employed.

Table 1 *Classification of liver trauma (after Calne* et al.[1]*)*

Grade	Injury
I	Capsular tear Minor bleeding that stops spontaneously or after a few simple sutures Parenchyma not damaged
II	Parenchymal damage Local haemostasis by careful suturing
III	Parenchymal damage Major haemorrhage from intrahepatic arteries and/or veins threatening life and producing shock
IV	Grade III injury with a tear of the inferior vena cava or major hepatic vessels

Results

There were 58 male and 15 female patients. The mean age was 30 (range 6–68) years; 55 (75 per cent) were in the range 16–39 years. The mechanism of injury was blunt in 44 cases (60 per cent) and penetrating in 29 (40 per cent). Road traffic accidents accounted for more than two-thirds (31 of 44) of the patients with blunt injury. Stabbing as a result of assault accounted for the majority of patients with penetrating injury (*Table 2*). Fourteen patients were transferred after initial resuscitation at outlying hospitals, but no patient underwent surgical intervention before transfer.

Conservative treatment

Seven patients (10 per cent) were managed successfully by non-operative means and discharged within 15 (mean 8) days of admission. None had been shocked at presentation and diagnostic peritoneal lavage was not carried out. In five patients the injury was blunt and in two knife wounds were responsible. The diagnosis of liver injury was made on the basis of the nature of the trauma and findings at ultrasonography. In addition to these seven cases, one patient subsequently underwent operation following failure of conservative management, 2 days after presentation with blunt abdominal injury. Although never hypotensive, she had required transfusion with 6 units blood and had developed worsening signs of peritoneal

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irritation on serial clinical examination The liver lacerations had stopped bleeding at the time of laparotomy, but cholecystectomy was undertaken for a perforated gallbladder. The postoperative course was complicated by a small bile leak, which resolved spontaneously

Ultrasonography was used to monitor the course of the hepatic lesion in all cases, supplemented by isotope scintigraphy and magnetic resonance imaging in one patient each. An expanding intrahepatic haematoma was monitored over 9 weeks in one patient and, although transfusion with 5 units blood was needed initially, operative intervention was avoided. The remaining patients had incurred minor lacerations, parenchymal contusions or haematomas, or subcapsular haematomas, which all remained silent without evidence of ongoing bleeding.

Table 2 *Mode of injury in 73 patients presenting with liver trauma*

	No
Penetrating	
Stabbing	
Assault	26 (36)
Self-inflicted	2 (3)
Accident in workplace	1 (1)
Blunt	
Road traffic accident	
Car occupant	18 (25)
Pedestrian	10 (14)
Motorcyclist	3 (4)
Fall from a height	6 (8)
Accident in workplace	6 (8)
Accident in home	1 (1)
Total	73 (100)

Values in parentheses are percentages

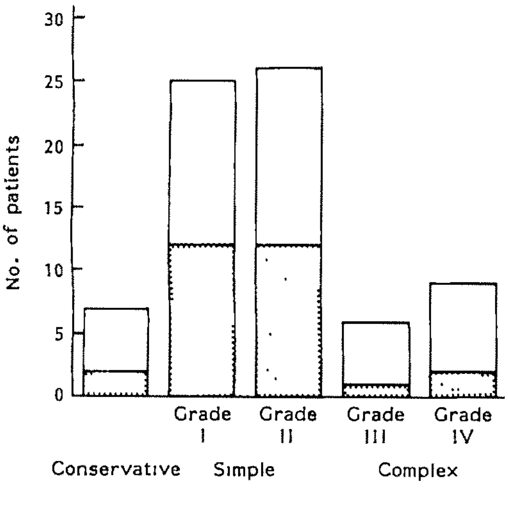

Figure 1 *Classification of 73 liver injuries presenting during 1980–1990* □, *Blunt injury,* ▨, *penetrating injury*

Simple injuries

There were 51 simple liver injuries, comprising 70 per cent of the patients in this series; 25 were grade I and 26 grade II. The mechanism of trauma was penetrating in 24 cases and blunt in 27 (*Figure 1*). Shock on admission was more common in blunt injuries (56 *versus* 21 per cent), which were associated with a higher median ISS than simple penetrating injuries (26·5 *versus* 10) (*Table 3*) There were associated major chest injuries and/or rib fractures in eight patients (33 per cent) with simple penetrating injuries compared with 17 (63 per cent) of those with simple blunt injuries. Isolated liver injuries were accordingly more common among patients with penetrating wounds than in those with closed injuries (50 *versus* 11 per cent).

Diagnostic peritoneal lavage was performed in 23 patients with blunt trauma (85 per cent), but in only five instances (21 per cent) of simple penetrating injury Where lavage was positive, the presence of a haemoperitoneum was confirmed at laparotomy in all cases. There were no instances of false-negative peritoneal lavage in this series (*Table 3*). There was no active bleeding from the liver laceration in 13 patients (54 per cent) with simple penetrating injury, and in 14 (52 per cent) with simple blunt injuries. In all cases the liver wound required no surgical intervention to achieve haemostasis, although drains were inserted, topical haemostatic agents applied or the laceration sutured.

Associated intra-abdominal organ damage requiring surgical repair complicated four cases (17 per cent) of simple penetrating injury (pancreas, stomach, small bowel and gallbladder laceration involved in one instance each), and suture of diaphragmatic lacerations was performed in a further five (21 per cent). Twelve (44 per cent) of the simple blunt injuries were associated with significant intra-abdominal organ damage (splenic tears or disruption in eight, gallbladder tears in two, mesenteric vessel avulsion in one, tears to the aorta and inferior vena cava at the level of the renal vessels with avulsion of the right renal artery in one). Postoperative complications were common (*Table 4*).

There were three deaths in the 51 patients with simple liver injury (mortality rate 6 per cent); all three occurred in patients who had suffered blunt trauma, but none was directly attributable to the liver wound. In two cases death occurred within 4 h of admission in patients with severe head and limb injuries, complicated in one by major chest injuries. In the other case, the patient presented in coma following an intracerebral bleed and was found to have severe pelvic and lower-limb fractures in association with a retroperitoneal haematoma. This patient developed bronchopneumonia, overwhelming sepsis and disseminated intravascular coagulopathy, and eventually died 32 days after initial laparotomy and suture of grade II liver lacerations.

Complex injuries

The 15 patients with liver trauma requiring complex surgical intervention comprised 21 per cent of this series; there were six grade III and nine grade IV injuries (*Figure 1*). Twelve cases (80 per cent) were the result of blunt injury and 12 patients were shocked on admission The median ISS was 29, ten

Table 3 *Presenting features and associated injuries of 73 patients with liver trauma*

Liver injury	No	Shock on admission	Median ISS	Positive diagnostic peritoneal lavage	Major chest injury and/or rib fracture	Associated abdominal injury
Simple						
Penetrating	24	5 (21)	10	5	8 (33)	4 (17)
Blunt	27	15 (56)	26·5	23	17 (63)	12 (44)
Complex	15	12 (80)	29	9	10 (67)	6 (40)
Conservative	7	—	7	—	1 (14)	—

Values in parentheses are percentages ISS, Injury Severity Score

Table 4 *Complications in 66 patients undergoing surgery for liver trauma*

	Simple		
	Penetrating ($n = 24$)	Blunt ($n = 27$)	Complex ($n = 15$)
Biliary fistula/bile leak	0	1	3
Progressive jaundice	0	3	2
Coagulopathy	0	3	1
Rebleeding	1	1	1
Intra-abdominal sepsis	0	0	2
Protracted ileus	1	2	0
Chest complications	8	15	7
Wound infection	1	0	1
Deep vein thrombosis	0	0	3
Pyrexia of unknown origin	1	1	0
Renal failure	0	0	1
Death	0 (0)	3 (11)	6 (40)
Complication rate in survivors (%)	46	79	89

Values in parentheses are percentages

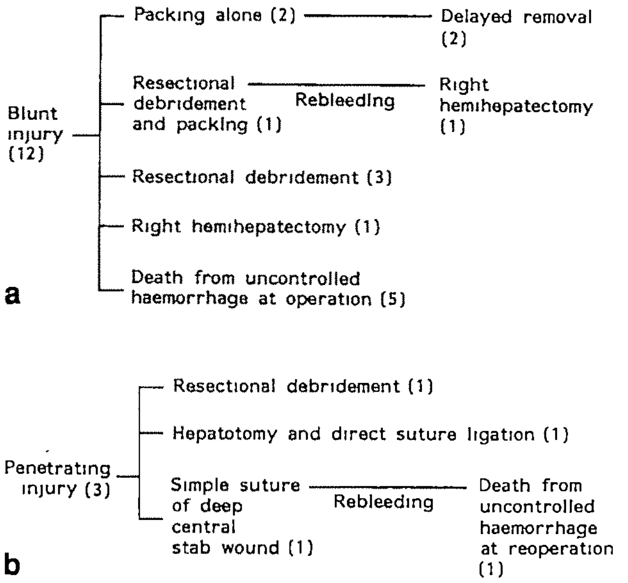
Blunt injury (12)
Packing alone (2)
Delayed removal (2)
Resectional debridement and packing (1)
Rebleeding
Right hemihepatectomy (1)
Resectional debridement (3)
Right hemihepatectomy (1)
Death from uncontrolled haemorrhage at operation (5)
a
Penetrating injury (3)
Resectional debridement (1)
Hepatotomy and direct suture ligation (1)
Simple suture of deep central stab wound (1)
Rebleeding
Death from uncontrolled haemorrhage at reoperation (1)
b

Figure 2 *Management of 15 patients with complex liver trauma.* **a** *Blunt injury,* **b** *penetrating injury*

patients (67 per cent) having associated major chest injuries and/or rib fractures (*Table 3*). Only one patient had an isolated liver injury. A positive peritoneal lavage was obtained in all nine cases (60 per cent) where immediate laparotomy was not clearly indicated because of shock or obvious gross abdominal injury.

A variety of techniques was employed to deal with these complex liver injuries (*Figure 2*). Thoracolaparotomy was carried out in five patients, with aortic cross-clamping on one occasion, and attempted cardiopulmonary bypass in another with severe chest injuries. Perihepatic gauze packing alone with delayed pack removal successfully controlled bleeding in a further two patients with grade III lacerations. Formal anatomical right hemihepatectomy was undertaken only twice: once in a patient treated initially by resectional debridement and perihepatic packing, where rebleeding followed pack removal on day 2; in the other case right hemihepatectomy was undertaken as a primary procedure following a massive stellate disruption of the right hemiliver. Both patients survived after a complicated postoperative course. Resection of traumatized liver was undertaken more commonly as resectional debridement, extending the parenchymal lacerations by hepatotomy and maintaining haemostasis by direct vascular suture ligation. Such resectional debridement was carried out initially in five of the patients who survived, although rebleeding occurred in one on pack removal (as described above). Atriocaval shunt insertion, hepatic vascular isolation techniques and hepatic artery ligation were not used in this series

Although major postoperative complications were seen in eight of the nine survivors, there were no late deaths. Biliary fistula with a subphrenic collection complicated two cases where packs had been used, but did not require reoperation. Clinically apparent coagulopathy with multiorgan failure, requiring renal dialysis and prolonged mechanical ventilation, occurred only once, following a right hemihepatectomy. All six patients with grade III injuries survived, but only three of the nine with liver injuries involving the inferior vena cava or major hepatic veins did so (overall mortality rate for complex liver injuries 40 per cent). All these deaths occurred as a result of uncontrolled haemorrhage from the liver bed and in the presence of severe coagulopathy but associated with major head, chest and/or limb injuries in four cases.

Discussion

The liver is the most commonly injured abdominal organ, although the frequency of splenic injuries is greater in patients with blunt abdominal trauma[3]. Major liver wounds are encountered relatively rarely by general surgeons working outside regional trauma centres and specialist hepatobiliary units. Indeed, the only published experience of major liver trauma in the UK comes from such tertiary referral centres[1,4,5] and this may not be representative of the type of injury seen in non-specialist units. Major hepatic injury may be extremely difficult to manage and is associated with high mortality rates. Although considerable improvement in outcome for even the most severe liver injuries has been documented over the past two decades in large American series[6–14], it is by no means certain whether this has resulted from a change in the management of such patients. Furthermore, it has not been ascertained whether this experience is shared in the UK, where major regional trauma centres are not established. The present study audits the experience of a variety of general surgical teams. Although these surgeons work in a major teaching hospital incorporating a trauma service, only a small number of cases of major liver trauma are encountered each year The overall mortality rate for hepatic trauma in the present series was 12 per cent, rising to 40 per cent for complex injuries and to 67 per cent where the inferior vena cava and/or hepatic veins were involved (grade IV injuries) The high mortality rate observed in complex injuries may be accounted for by the high proportion of patients with trauma secondary to blunt injury, and may reflect the severity of associated injuries. The mortality rate is similar to those of other centres[1,6–15] and confirms that hepatic vein injury carries a mortality independent of the parenchymal damage.

Accurate comparison of reports on liver trauma remains difficult long after the recognition of the need for a universally accepted standard classification of liver injury. Various systems of classification are in use, based on the extent of the initial hepatic injury and the type of operative intervention needed[1,8–12,15], whereas others have proposed an operative scheme based on the segmental anatomy of the organ[16]. The classification popularized by Calne *et al.*[1] is simple to apply retrospectively. It facilitates further stratification into simple and complex forms of operative management, and is preferable to other more complicated multicategory classifications for the purposes of analysis[10,17].

This study has confirmed the observation[6,7,12,18–20] that a substantial proportion of simple blunt liver injuries will have stopped bleeding at the time of laparotomy. Most of these patients underwent diagnostic peritoneal lavage, but it seems likely that the finding of blood in the peritoneal cavity not infrequently resulted in unnecessary laparotomy. It is now well documented that selected blunt liver injuries can be treated without operation, and blunt hepatic trauma in children appears especially suited to a conservative approach[21–26]. As experience with the non-operative management of adult blunt liver trauma has accumulated and gained wider acceptance[5,15,19,20,27–33], it has been shown that 20–34 per cent of all patients with liver trauma may be successfully treated in this way in centres with appropriate expertise[19,20]. Only 10 per cent of patients in the current series were treated without operation, suggesting that a number were submitted to unnecessary laparotomy. Nevertheless, some have expressed concern at the hazards of delayed operative intervention[34], while the risk of undetected gastrointestinal disruption has led others to conclude that non-operative management of blunt abdominal trauma 'as a matter of routine' is not justified[35]. The five patients with blunt liver injury who underwent successful non-operative treatment in the present series all fulfilled the criteria of haemodynamic stability with no clinical indication for laparotomy. These injuries comprised intrahepatic and subcapsular haematomas as well as minor hepatic contusions, and were monitored by ultrasonography, although computed tomography (CT) provides superior definition for imaging abdominal injuries[5,19–21,25,30–33]. The risk that hollow viscus injury might escape timely detection was illustrated by the patient in whom the attempted non-operative management of a grade I liver injury led to delayed recognition of an associated gallbladder rupture; this was followed by a complicated postoperative course. Angiography with transcatheter hepatic artery embolization has been shown to be effective in the treatment of expanding intrahepatic haematomas[27] and may have modified the progress of the patient with significant transfusion requirements.

The policy of diagnostic peritoneal lavage and laparotomy appears to have been appropriate for the majority of patients with simple blunt liver injuries presenting to this hospital over the past 10 years. More than half of these patients were initially shocked, major multisystem trauma was common, and associated intra-abdominal injuries were seen in 44 per cent of laparotomies – factors that discourage non-operative management[20]. The option of such management for selected cases of isolated minor liver injury requires careful and experienced evaluation of the abdomen by ultrasonography and CT. A strict treatment protocol should be followed and will include intensive care monitoring, serial clinical examination, expertise with contrast-enhanced CT and visceral angiography, and long-term follow-up[19,20,33]. These criteria render the non-operative management of blunt liver trauma unsuitable in centres without the necessary facilities and experience. A non-operative approach may be better followed in a referral centre with appropriate available expertise[5,11,20,22,30,31].

The patterns of management clearly varied for blunt and penetrating injury in this series. The frequent practice of mandatory exploratory laparotomy for simple penetrating injuries appears to have resulted in a high number of unnecessary laparotomies, with significant postoperative morbidity mainly from chest infection and which could not always be attributed to an associated chest injury. It has been shown that 50–70 per cent of patients with penetrating abdominal stab wounds can be treated conservatively according to clinical criteria[36,37], and one-third of penetrating liver wounds were successfully treated without operation by serial clinical examination in the one prospective trial that has evaluated non-operative management by clinical means[38]. The diaphragmatic lacerations seen in 21 per cent of patients with simple penetrating liver injury in this centre were not included for analysis as associated intra-abdominal organ injuries, although the non-operative management of stab wounds to the liver may result in late presentation of internal hernias through the unsutured diaphragmatic defect.

The simple methods employed to achieve haemostasis with both blunt and penetrating grade I and II injuries were effective in that in these patients there were no deaths related to the liver injury, and none required reoperation for rebleeding from the hepatic wound. The use of interrupted deep 'liver sutures' has been condemned in the past for fear of haemobilia or intra-abdominal sepsis secondary to liver necrosis, although the risk of these complications may have been overstated[12,18]. The continued use of appositional liver sutures for simple injuries is supported, although it is important to differentiate these wounds from those that clearly require more complex surgical intervention or temporary measures such as packing. The danger of suturing the entry site of an actively bleeding central penetrating liver wound is illustrated by the patient in whom rebleeding ensued, with the development of a bursting-type intrahepatic haematoma. It would have been more appropriate to have explored the wound, extending the laceration and gaining access by hepatotomy, to achieve haemostasis by direct suture ligation of the bleeding vessels. This approach for deep lacerations as popularized by Pachter and colleagues[39] and recommended by others[6,9,10,12,17] nevertheless has its detractors[13], who cite the risks of provoking substantial haemorrhage and technical difficulty in inaccessible locations. There seems little doubt that hepatotomy with direct vascular suture ligation may be especially useful with complex penetrating wounds, and was used effectively on one such occasion where the left hepatic vein had been transected. Its role in blunt injuries is, however, not so well defined and requires further evaluation[40].

Surgical restraint in the management of liver injury has been strongly advocated in recent years, with the techniques of perihepatic gauze packing, hepatic artery ligation and resectional debridement gaining acceptance. Temporary liver packing allows time for correction of hypovolaemia, coagulopathy, acidosis and hypothermia, and allows transfer to specialist care if necessary[1,5,9,10,14,15,18,41]. High rates of intra-abdominal sepsis of up to 83 per cent have been reported[11,42], however, and this is confirmed in the present series, in which two of the three patients with complex liver injury treated by packing developed an intra-abdominal collection and biliary fistula.

Despite earlier enthusiasm for anatomical hepatic resections in major liver trauma[4], the associated mortality has resulted in the widespread adoption of a more conservative approach. As many as 14 per cent of all liver injuries[40] and 33 per cent of major liver injuries[14] may require some form of resection, and in most instances resectional debridement is preferable to formal hepatectomy[6–10,12,15,18]. Liver resection was undertaken in just six cases (8 per cent) without mortality, although with considerable postoperative morbidity. A factor consistently related to death from liver trauma is failure to achieve control of bleeding in complex injuries associated with hepatic vein or vena cava tears. Unfortunately, evidence to support the use of hepatic vascular isolation with atriocaval shunting[43], and hepatotomy with direct vascular suture ligation[39], is lacking. Mortality rates for such injuries remain high, and the successful management of these relatively uncommon injuries requires the expertise of a specialist team or major trauma centre.

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Abdominal inflammatory myofibroblastic tumours in children

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Inflammatory myofibroblastic tumours (inflammatory pseudotumours) occurring at intra-abdominal sites in children have rarely been described. This paper reports three patients with this tumour, two of whom presented with fever, anaemia and an abdominal mass, the third with chronic duodenal obstruction. All had experienced significant weight loss. At operation, each had a large fibrous tumour (7–18 cm in diameter) originating from the transverse mesocolon, small bowel mesentery and duodenum respectively. Intraoperative frozen section histological examination in one patient was misinterpreted as a sarcoma. All the lesions were judged to have been completely excised, but one was ruptured during operation and the patient subsequently developed recurrent tumour nodules. Abdominal inflammatory myofibroblastic tumours are rare. They may be suspected before operation but their clinical, radiological and pathological features may be confused with those of malignancy. Complete excision is necessary to avoid local recurrence.

Inflammatory myofibroblastic tumours are rare proliferative lesions clinically resembling true neoplasms but histologically distinct. Their classification is controversial and confusing, and a variety of synonyms exists, including inflammatory pseudotumour and plasma cell granuloma[1–4]. The myofibroblast is now considered the predominant cell type and the lesion believed to be reactive rather than neoplastic[5–7]. The tumours are well circumscribed but rarely encapsulated and consist of a fibrovascular stroma composed of compact bundles of mature spindle cells (myofibroblasts) with an admixture of plasma cells, lymphocytes and foamy histiocytes[2–4].

Inflammatory myofibroblastic tumours are well described in the lung and upper respiratory tract of young adults and children[1,8], but may occur at any age and affect any organ system[4,7–12]. Intra-abdominal lesions are rare and have been recognized in children only in recent years. Three children with abdominal inflammatory myofibroblastic tumours referred during the past 5 years are described.

Patients

Patient 1

A 5-year-old boy with a 2-month history of malaise and intermittent fever was referred for investigation of a large firm mobile left-sided abdominal mass. Investigations revealed microcytic hypochromic anaemia (haemoglobin level 6·6 g/dl, mean corpuscular volume (MCV) 65 fl, mean corpuscular haemoglobin (MCH) 19·9 pg) and thrombocytosis (platelet count 708 × 10^9/l). The plasma albumin level was 22 g/l and globulins 59 g/l (normal range 30–47 g/l). Ultrasonography confirmed a hypoechoic mass anteromedial to the left kidney and crossing the midline. Results of skeletal radiography, radionuclide bone scan and bone marrow aspirate were all normal.

At operation, a large lobulated mass (12 × 10 × 6 cm) originating at the base of the transverse mesocolon and firmly adherent to the duodenojejunal flexure was identified. The tumour was resected with adjacent jejunum and intestinal continuity restored. After operation, pyrexia and haematological abnormalities resolved. Some 2 months later, at operation for adhesive bowel obstruction, no residual tumour was seen. The boy remains well 5 years later.

Patient 2

A previously fit 8-year-old girl was referred with a 1-week history of intermittent fever and vague abdominal pain. On examination, she had a large firm mobile central abdominal mass. Investigations showed mild microcytic hypochromic anaemia (haemoglobin 10·1 g/dl, MCV 76 fl, MCH 24·8 pg) and hypoalbuminaemia (30 g/l). Ultrasonography confirmed a solid mass lying anterior to the great vessels but separate from the kidneys and liver.

At laparotomy a large lobulated mass was found arising from the small bowel mesentery and densely adherent to the superior mesenteric vessels. Intraoperative frozen section biopsy was reported as a rhabdomyosarcoma. The mass was inadvertently split during the operation without obvious tumour spillage and complete macroscopic clearance was achieved in continuity with a right hemicolectomy. The resected tumour was multilobulated, measured 18 × 13 × 5 cm and weighed 900 g; its cut surface showed fleshy pink areas and interlacing fibrous bundles.

The child's fever and haematological abnormalities resolved but 5 months later she developed recurrent fever and abdominal pain associated with weight loss, anaemia (haemoglobin 7·1 g/dl), thrombocytosis (platelet count 850 × 10^9/l), hypoalbuminaemia (24 g/l) and hyperglobulinaemia (53 g/l). Ultrasonography demonstrated a 5-cm mass adjacent to the bladder. A second laparotomy revealed multiple pink tumour nodules within the greater omentum but no lesion at the previous site of resection. The omentum and tumour nodules were removed. The patient subsequently required two further operations for adhesive intestinal obstruction; at the first a small nodular mesenteric recurrence was excised but at the second operation 1 year later no tumour was evident. During the past 3 years she has remained well.

Patient 3

A previously well 5-year-old girl presented with a 1-month history of progressive non-bilious vomiting and profound weight loss. A barium meal showed a large dilated stomach with copious residue and poor gastric emptying; abdominal ultrasonography revealed a filling defect in the second part of the duodenum. After a short period of intravenous nutrition, a laparotomy was performed. A large lobulated tumour occupying the second part of the duodenum was biopsied and a feeding jejunostomy inserted. Histology was that of an inflammatory pseudotumour and, after 1 month of enteral feeding, definitive surgery was performed. Preoperative computed tomography demonstrated the anatomy of the tumour, which was enhanced after administration of intravenous contrast (*Figure 1*).

At operation, a tumour mass measuring 7 × 4 × 4 cm was identified in the region of the second part of the duodenum and pancreatic head (*Figure 2*). A Whipple pancreaticoduodenectomy was performed with standard reconstruction. The resected tumour extended through the submucosa and muscularis into the serosa. The patient made an uncomplicated recovery and remains well 9 months later.

In all three patients, tumour marker studies and tissue and blood microbiological cultures were negative.

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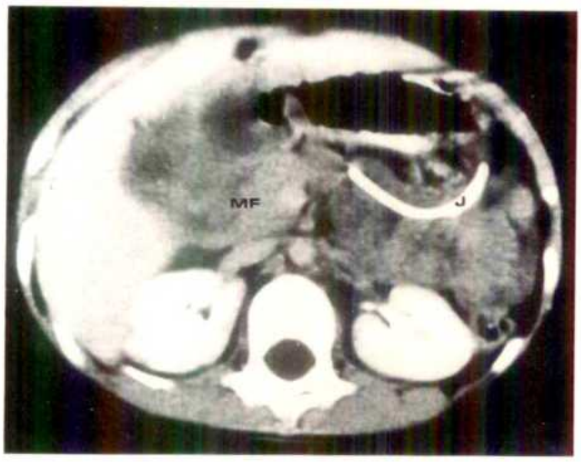

Figure 1 *Contrast-enhanced computed tomography in patient 3 showing the inflammatory myofibroblastic tumour (MF) in the region of the pancreatic head. The feeding jejunostomy tube (J) is also visible*

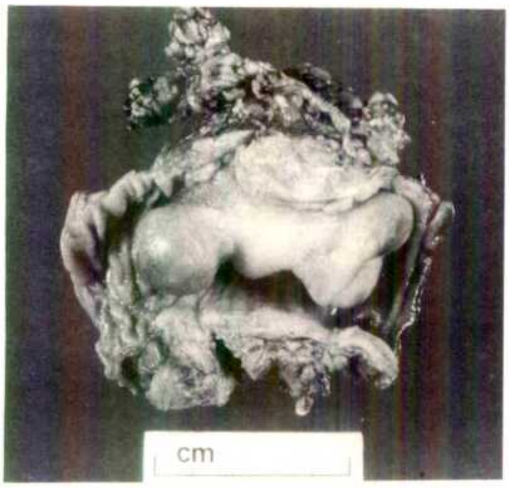

Figure 2 *Resection specimen from patient 3 showing the sessile polypoid inflammatory myofibroblastic tumour protruding into the duodenal lumen and extending into its wall*

Results

Pathology

Microscopically, these masses were composed of an admixture of proliferating spindle cells and chronic inflammatory cells embedded in a variably vascular stroma that ranged from being loosely myxoid to densely collagenous (*Figure 3*). Some of the spindle cells were large with eosinophilic nucleoli and contained moderate amounts of pink cytoplasm, but there were no cytoplasmic striations indicative of rhabdomyoblastic differentiation. The spindle cells stained with vimentin but were uniformly negative with desmin, leucocyte common antigen and S-100 antigen (excluding rhabdomyosarcoma, lymphoma and melanoma respectively). There was no evidence of pleomorphism or hyperchromasia and no abnormal mitotic figures. The inflammatory cells were a polymorphous mixture of mature plasma cells and T and B lymphocytes with scattered eosinophils and mast cells. Foamy histiocytes were present focally and lymphoid follicles diffusely distributed. A small number of plasma cells contained intracellular Russell bodies, indicative of immunoglobulin secretion. Electron microscopy (patient 2) showed that most of the spindle cells had ultrastructural features of myofibroblasts, although some were fibroblasts.

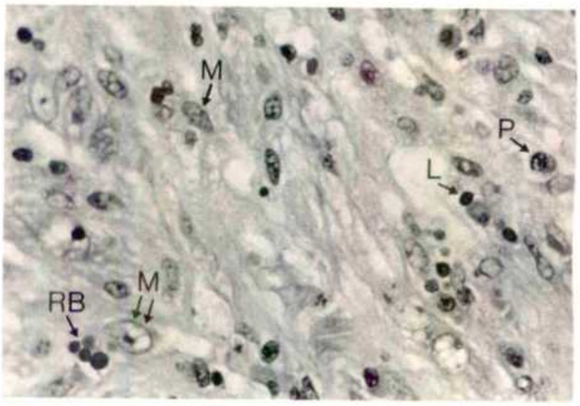

Figure 3 *Microscopic appearance of an inflammatory myofibroblastic tumour demonstrating plasma cells (P) with associated Russell bodies (RB), lymphocytes (L) and both spindle-shaped (M →) and plump (M ⇉) myofibroblasts. (Haematoxylin and eosin stain, original magnification × 400)*

Discussion

A total of 21 children, predominantly female, with inflammatory myofibroblastic tumours affecting intra-abdominal sites have been reported (*Table 1*)[13–23]. These tumours are often large and arise from a vascular pedicle or infiltrate the structure of origin. The tumour usually has a homogeneous consistency, although areas of haemorrhage, necrosis or calcification may be found[2,15,18,21]. Multicentric lesions are rare[4,7,8]. There are no reports of malignancy arising in an inflammatory myofibroblastic tumour; nevertheless, the clinical, radiological and histological features of these may cause confusion with malignant lesions.

Two of the patients reported presented with fever, anaemia, thrombocytosis and hyperglobulinaemia. Similar features, including weight loss and a raised erythrocyte sedimentation rate, have been reported in many of the children with abdominal inflammatory myofibroblastic tumours[2,7,17,21–23]. White cell counts are conspicuously normal except for the occasional patient with eosinophilia. The anaemia is typically microcytic and hypochromic but unresponsive to iron therapy. These systemic features resolve after tumour excision but may enable the diagnosis to be suspected before operation.

Misdiagnosis has led some patients to be inappropriately treated with chemotherapy and radical surgery before reclassification[2,6,21]. Histologically, the high cellularity with large, spindle or plump active myofibroblasts with prominent nucleoli can cause confusion with malignancy, in particular rhabdomyosarcoma[2,6]. However, the lack of atypia, hyperchromasia and abnormal mitotic figures are pointers toward a benign lesion. Inflammatory myofibroblastic tumours should be diagnosed by routine staining because special stains and immunocytochemistry can be misleading[6]. Preliminary biopsy and full histological evaluation is recommended in cases where resection may be particularly hazardous.

Other reasons for confusion of inflammatory myofibroblastic tumours with neoplasia include their capacity for local tissue infiltration, occasional rapid growth and the development of local recurrence. Mediastinal and oesophageal involvement from adjacent pulmonary pathology appears to be particularly aggressive[24–26]. In patient 2, seeding may have followed inadvertent tumour rupture during the original resection; one previous report may represent a similar process[27]. Local recurrence after incomplete excision is recognized[4,8,21,28], may occur many years later[28] and may be fatal[29]. This underlines the importance of complete surgical resection whenever possible.

The management of inflammatory myofibroblastic tumours is complicated by their unpredictable natural history, which ranges from spontaneous regression through gradual enlarge-

Table 1 *Abdominal inflammatory myofibroblastic tumours in children*

Reference	Year	Country	Age	Sex	Tumour size (cm)	Tumour site	Treatment	Outcome
Haith *et al.*[13]	1964	USA	6 years	M	3	Common bile duct	Resection	Well
Luthi *et al.*[14]	1968	Switzerland	16 years	M	7	Transverse mesocolon	Resection	Well
Hertzer *et al.*[15]	1971	USA	13 months	F	—	Liver (central)	Steroids	Well 3 years later
Wu *et al.*[16]	1973	USA	14 years	F	7	Gastric antrum	Resection	Well
Someren[3]	1978	USA	4 years	M	8	Liver (right lobe)	Resection	Well
Pisciotto *et al.*[17]	1978	USA	2 years	F	7	Terminal ileum	Resection	Well
Abrebanel *et al.*[18]	1984	Israel	12 years	F	10	Pancreas	Resection	Well
Heneghan *et al.*[19]	1984	USA	8 years	F	—	Liver (right lobe) and porta hepatis	Liver transplantation	Well
Day *et al.*[2]	1986	USA	5 years	M	10	Ileal mesentery	Resection	Well
			9 years	F	7	Ileal mesentery	Resection	Well
			7 years	F	8	Mid-small bowel mesentery	Resection	Well*
Tanyel *et al.*[20]	1987	Turkey	11 months	M	9	Mid-ileum	Resection	Well
Scott *et al.*[21]	1988	Canada	2 years	F	—	Pancreas	Resection	Well
			2 years	F	—	Sigmoid mesentery	Resection	Well
Maves *et al.*[22]	1989	USA	5 years	F	8	Gastric fundus	Resection	Well
			18 months	F	—	Gastric	Resection	Late death†
Lin *et al.*[23]	1990	Taiwan	2 years	F	4	Gastric antrum	Resection	Well
			8 years	F	6	Greater omentum	Resection	Late death†
			7 years	F	6	Peritoneum (right iliac fossa)	Resection	Well
Tang *et al.*[7]	1990	USA	10 months	F	11	Mesoappendix	Resection	Well
			5 years	F	10	Gastric	Resection	Well

All resected tumours were completely excised and no such patients had recurrent disease after follow-up ranging from 2 months to 6 years. *Initially misdiagnosed as rhabdomyosarcoma. †Not directly related to inflammatory myofibroblastic tumours

ment to rapid growth with local invasion[8,10,26,28–31]. Tumour resolution or regression has been reported after radiotherapy[8,25,32], although radioresistance has also been described[7,24]. There are anecdotal reports of chemotherapy with no clear benefit[2,6,25] and steroid therapy with variable results[1,33,34].

The aetiology of inflammatory myofibroblastic tumours is unknown; many authors have postulated a postinflammatory process[12,16,20,35]. However, in most cases there is no identifiable precipitating factor. Evidence to support a directly infectious aetiology is scanty, but an immunological pathogenesis remains possible.

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Serum tumour necrosis factor alpha and insulin resistance in gastrointestinal cancer

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Cancer cachexia may be mediated by endogenous peptides such as tumour necrosis factor alpha (TNF-α). Insulin resistance occurs in these patients, and is also seen experimentally with TNF-α administration. In this study, insulin sensitivity and energy metabolism were measured in 11 patients with gastrointestinal cancer and ten controls, using the euglycaemic glucose clamp and indirect calorimetry. Patients with cancer were significantly more insulin resistant than controls ($P < 0{\cdot}01$) and in such patients insulin resistance correlated with serum TNF-α level ($r_S = 0{\cdot}74$, $P < 0{\cdot}01$). Fasting insulin levels also correlated inversely with insulin sensitivity ($r_S = -0{\cdot}62$, $P = 0{\cdot}003$). These results suggest a possible association between endogenous TNF-α production and insulin resistance in patients with gastrointestinal cancer.

Malnutrition caused by mechanical obstruction of the gastrointestinal tract, loss of appetite and abnormalities of host metabolism is common in gastrointestinal cancer[1]. Aberrations of carbohydrate, fat and protein metabolism have been described in detail in the cancer-bearing host[2], with resistance to the anabolic effects of insulin playing a prominent role. These abnormalities may be mediated indirectly by endogenous peptides, such as tumour necrosis factor alpha (TNF-α), activated during immune and inflammatory responses to a variety of stimuli[3]. TNF-α fulfils Koch's postulates as a mediator of fatal sepsis[4] and has also been implicated, when produced in lesser amounts, as a possible mediator of cancer-associated cachexia[5].

The euglycaemic glucose clamp (EGC) is an established method of assessing insulin resistance *in vivo*[6]. The aim of this study was to measure insulin resistance and energy metabolism in patients with gastrointestinal cancer and correlate these with circulating TNF-α levels.

Patients and methods

Subjects

Eleven patients with gastrointestinal cancer (*Table 1*) and ten control subjects matched for age and weight were studied after an overnight fast. Subjects were excluded if they had had surgery, chemotherapy or radiotherapy within 3 months of the study, if receiving inhaled or oral corticosteroids, or if they had diabetes or sepsis. Control subjects had no history of malignancy or other acute or chronic illness, with the exception of stable non-disabling intermittent claudication. Ethical committee approval was obtained and all subjects gave written informed consent.

Body surface area was estimated from height and weight measurements; total body fat and fat-free mass were derived from triceps, biceps and subscapular skinfold thickness[7]. Measured weight was subtracted from recalled well weight to calculate the percentage weight loss.

Euglycaemic glucose clamp

Subjects underwent a 2-h EGC, after the method of De Fronzo *et al.*[6]. A primed continuous insulin infusion (20 milliunits/m^2/min) was administered via an antecubital vein for the 2-h study period. Using the heated hand technique[8], arterialized blood samples were drawn at 10-min intervals for rapid glucose measurement by the glucose oxidase method. Euglycaemia was maintained by infusing 25 per cent dextrose solution at a rate adjusted according to a computerized iterative servocontrol formula. Samples were also collected at 30-min intervals for serum insulin levels, measured by radioimmunoassay (Amersham Australia, Sydney, Australia). The amount of glucose required to maintain euglycaemia (designated 'metabolized glucose') under these conditions is inversely related to insulin resistance[6].

Table 1 *Diagnosis, stage of disease and weight loss in patients with gastrointestinal cancer*

Patient no.	Primary tumour	Stage of disease	Weight loss (%)
1	Colon	Dukes' B	0
2	Rectum	Local recurrence	0
3	Colon	Dukes' 'D'	14
4	Colon	Dukes' 'D'	0
5	Pancreas	Metastatic	16
6	Rectum	Dukes' 'D'	0
7	Colon	Dukes' A	0
8	Colon	Dukes' B	0
9	Stomach	Metastatic	13
10	Rectum	Dukes' B	0
11	Colon	Dukes' C	0

Indirect calorimetry

Indirect calorimetry using the ventilated hood method[9] was undertaken on all subjects during the second hour of the clamp study. These measurements were used to derive instantaneous resting energy expenditure, glucose oxidation and fat oxidation[10]. Glucose storage was derived by subtracting oxidized from metabolized glucose. Urinary nitrogen excretion was measured and used to estimate net protein oxidation[11].

Serum tumour necrosis factor alpha assay

Serum was collected from each subject at the beginning of the study and stored at −70°C until immunoradiometric assay (Medgenix, Fleuris, Belgium) as described by McCall *et al.*[12]. The assay is sensitive to 1 pg/ml recombinant TNF-α. During storage, one unintentional freeze–thaw cycle (to 4°C) occurred owing to freezer malfunction. All samples were affected.

Statistics

Unpaired group data were compared using Student's unpaired *t* test and associations between biological variables tested using Spearman's signed rank correlation coefficient (r_S).

Results

Patients and controls were not significantly different with respect to age (mean(s.e.m.) 67(3·1) *versus* 60(3·8) years), sex (F:M 5:6 *versus* 4:6), weight (mean(s.e.m.) 72(6·2) *versus* 75(5·1) kg), total body fat as a fraction of weight (mean(s.e.m.) 28·1(1·8) *versus* 27·3(2·6) per cent) or baseline levels of glucose (mean(s.e.m.) 4·3(0·1) *versus* 4·4(0·1) mmol/l) and insulin (mean(s.e.m.) 13·1(2·3) *versus* 10·4(1·4) milliunits/l).

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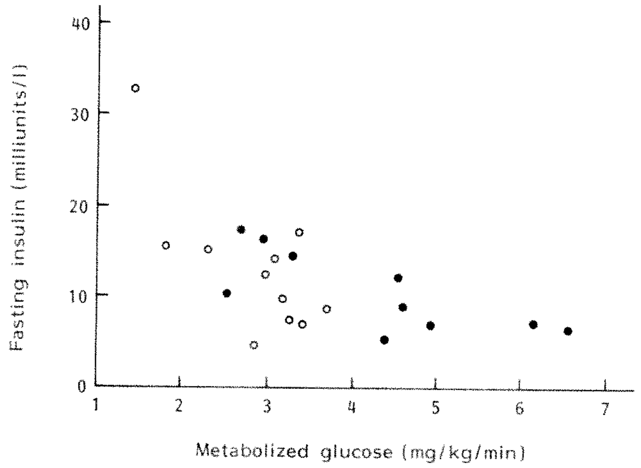

Figure 1 *Correlation between fasting insulin levels and metabolized glucose for 11 patients with cancer (○) and ten controls (●).* $r_S = -0·62$, $P = 0·003$

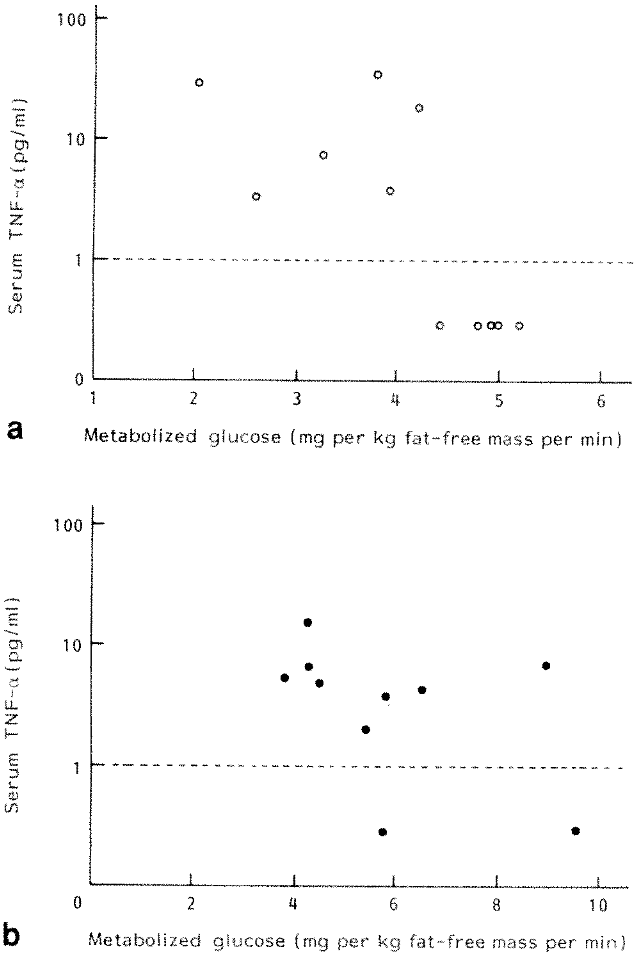

Figure 2 *Correlation between serum tumour necrosis factor alpha (TNF-α) levels and metabolized glucose for* **a** *11 patients with cancer* ($r_S = -0·74$, $P < 0·01$) *and* **b** *ten controls* ($r_S = -0·17$, $P = 0·65$). *The line at 1 pg/ml represents the TNF-α assay detection limit*

Table 2 *Results of metabolic measurements*

	Controls ($n = 10$)	Patients with cancer ($n = 11$)	P*
Metabolized glucose (mg/kg/min)	4·3(0·4)	2·8(0·2)	<0·01
Glucose oxidation (mg/kg/min)	2·0(0·2)	1·8(0·2)	0·54
Glucose storage (mg/kg/min)	2·3(0·4)	1·1(0·3)	0·02
Protein oxidation (g/day)	29·7(2·0)	37·1(4·0)	0·10
Fat oxidation (mg/kg/min)	0·6(0·08)	0·7(0·12)	0·69
Resting energy expenditure (kJ/kg/day)	148·7(5·0)	147·0(8·0)	0·89

Values are mean(s.e.m.). *Student's unpaired *t* test

Mean(s.e.m.) insulin levels during the EGC were 69(6·5) and 67(4·5) milliunits/l for patients and controls respectively, which is in the upper physiological range. Fasting insulin levels correlated inversely with metabolized glucose ($r_S = -0·62$, $P = 0·003$) (*Figure 1*). There was no correlation between fasting glucose levels and metabolized glucose. Metabolized glucose values were significantly lower in patients with cancer than in controls, reflecting a state of insulin resistance (*Table 2*). This was due mainly to an apparent shortfall in glucose storage, whereas glucose oxidation was not significantly different.

Although mean(s.e.m.) serum TNF-α levels were higher in patients with cancer than in controls (8·9(3·9) *versus* 4·9(1·5) pg/ml), this difference was not significant ($P = 0·38$). Nevertheless, there was a significant inverse relationship between serum TNF-α levels and metabolized glucose in patients with cancer ($r_S = -0·74$, $P < 0·01$) but not control subjects ($r_S = -0·17$, $P = 0·65$) (*Figure 2*). Resting energy expenditure was similar in patients and controls, and no association with serum TNF-α levels was found.

To test whether weight loss in itself might be responsible for the observed differences between patients with cancer and controls, the calculations were repeated after excluding the three patients with cancer who lost weight. Patients with cancer whose weight was stable remained significantly more insulin resistant than controls (mean(s.e.m.) metabolized glucose 2·9(0·2) *versus* 4·3(0·4) mg/kg/min, $P < 0·01$), and the inverse relationship between metabolized glucose and serum TNF-α levels was retained ($r_S = -0·86$, $P = 0·006$).

Discussion

In an elaborate study using a multiple-dose EGC technique, Copeland *et al.*[13] showed that insulin responsiveness was impaired in patients with colorectal cancer. The present study using a single-dose EGC cannot distinguish insulin responsiveness (postreceptor mechanism) from insulin sensitivity (prereceptor mechanism). Nevertheless, the present results are consistent with others in demonstrating significant insulin resistance in patients with gastrointestinal cancer[13–15].

Concurrent use of indirect calorimetry in this study has enabled metabolized glucose to be partitioned into glucose oxidation and, by difference, glucose storage. Glucose oxidation rates and resting energy expenditure were not significantly different in the patients with cancer and controls, which is consistent with previous studies[16,17]. The reduction in glucose storage appears to account for most of the shortfall in metabolized glucose observed in patients with cancer (*Table 2*), but this depends on the assumption that hyperinsulinaemia inhibits endogenous glucose production equally in both patients with cancer and controls. This assumption may not be valid since gluconeogenesis in the presence of an adequate carbohydrate load is itself partly a manifestation of insulin resistance, and cannot be entirely suppressed by glucose infusion or total parenteral nutrition in patients with gastrointestinal cancer who are losing weight[14,18]. However, complete suppression of endogenous glucose production in patients with cancer who are losing weight was reported using high physiological concentrations of insulin[15], similar to those used in the present study.

Driven by glucose–lactate recycling and availability of amino acid substrates derived from net protein breakdown, endogenous glucose production is reflected in altered protein kinetics[19]. *Table 2* shows that estimated net protein oxidation was indeed higher in patients with cancer, although this was not statistically significant. In the present study therefore, the difference between metabolized glucose in patients with cancer and controls could reflect reduced glucose storage, ongoing endogenous glucose production, or both. Simultaneous radioisotope studies with the EGC and calorimetry would be necessary to resolve this question[6,15].

Interestingly, there was no correlation in this study between tumour stage or degree of weight loss and insulin resistance. Even after exclusion of the three patients with cancer who lost weight, the patients with stable weight remained significantly more insulin resistant than controls. This confirms the observation of Copeland *et al.*[20] that metabolic abnormalities precede weight loss. Effective compensatory mechanisms, such as the increase in baseline insulin levels found in association with insulin resistance, may therefore be operational (*Figure 2*).

Although serum TNF-α levels were modestly raised in patients with cancer, the wide variance and small sample size rendered any difference insignificant, in contrast to results of a previous study[12]. The effects of an additional thaw during sample storage cannot be known with certainty, although maintenance of TNF-α immunoreactivity in stored sera through three successive freeze–thaw cycles has been reported[21]. Maintenance of TNF-α immunoreactivity in tissue samples subjected to several freeze–thaw cycles has also been observed by the authors[22].

In vitro, TNF-α induces glycogen depletion, increased lactate production[23] and postreceptor insulin resistance[24], mechanisms also exhibited[25] in trauma and sepsis where TNF-α plays an acknowledged major role in the pathophysiology[4]. Exogenously administered TNF-α raises skeletal muscle amino acid efflux and alters glucose handling[26,27]. Anti-TNF-α antibodies ameliorate the metabolic consequence of the tumour-bearing state in mice[5] with undetectable circulating TNF-α levels. The present study demonstrates an association between modest levels of circulating TNF-α and insulin resistance in patients with cancer *in vivo*. This correlation is not weakened by excluding patients with weight loss, confirming that weight loss *per se* is not responsible for the observed association. Such modest levels of TNF-α would seem unlikely to be the sole mediator of major metabolic disturbances. Nevertheless, TNF-α may be important, either in an active or permissive sense, in establishing an environment in which metabolic aberrations persist, to the detriment of the host. Although much of the evidence remains circumstantial, even anecdotal[28], fresh approaches to nutritional therapy for patients with cancer may result from exploring these mechanisms.

Acknowledgements

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Incidence and prognosis of Krukenberg tumour in Northern Ireland

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The case notes of 15 patients with Krukenberg tumours were studied to determine the incidence, presentation, clinical findings and prognosis of the disease in Northern Ireland. Patients tended to be young and premenopausal. A short history of abdominal pain was the most frequent presenting complaint, abdominal swelling being second. Menstrual irregularities occurred infrequently and no patient was virilized. Tumours tended to be large, bilateral and associated with ascites. The stomach was the commonest primary site. The overall prognosis was poor, especially if the primary tumour remained covert at the time of diagnosis. The prognosis was unaffected by subsequent discovery of the primary source; extensive investigation is inconvenient for the patient and wasteful of resources. The incidence of the tumour in Northern Ireland was 0·16 per 100 000 per annum: it will be rarely encountered by general surgeons.

The Krukenberg tumour is an uncommon variety of metastatic cancer to the ovary, first described by Friedrich Krukenberg[1] in 1896. He mistakenly thought the lesion to be a primary ovarian tumour of uncertain classification and named it 'fibrosarcoma ovarii mucocellulare carcinomatodes', believing it to be a sarcoma.

In 1902, Schlagenhaufer[2] established that these cancers were of epithelial origin and were secondary tumours. Some authors include all metastases to the ovary arising from an adenocarcinoma anywhere in the body[3]; others limit the definition to those metastases secondary to a gastrointestinal primary[4]. This accounts for some of the differences in the reported incidence of this tumour.

The incidence and experience of Krukenberg tumour was reviewed in Northern Ireland, where the population is ethnically the most homogenous in the UK and has remained relatively constant[5] over the past 20 years.

Patients and methods

The pathology records of the Royal Victoria and Belfast City Hospitals were searched from 1970 to 1984 inclusive. Krukenberg tumour was the reported diagnosis in 26 patients. Only those that fulfilled the diagnostic criteria of Novak and Gray[6] were accepted. These criteria, verified by Woodruff and Novak[7] as well as Hale[8], are now accepted by the World Health Organization[9] for the classification of Krukenberg tumours: the tumour must be in the ovary, with intracellular mucin formation evidenced by the presence of signet cells and a diffuse stromal reaction. The histology was re-examined in cases where these criteria were not specified. Fifteen patients were identified with tumours that fulfilled the above criteria. The clinical findings, treatment, progress and 5-year survival of these patients was determined.

Results

The 15 patients were aged between 37 and 73 (mean 50·3) years at the time of diagnosis. Nine were premenopausal.

The commonest presenting complaint was abdominal pain (*Table 1*). In seven patients this pain was related to the ovarian pathology, i.e. crampy lower abdominal pain, dragging sensation in the lower abdomen, or low backache. The history was usually short, a few weeks or months, the longest being 5 months. One patient had a 1-week history of lower abdominal pain that suddenly became severe 4 h before admission. She had a torsion of the involved ovary. Of those who presented with pain related to the primary malignancy, one was admitted acutely with obstruction and the others had a history of pain lasting several months.

Seven patients presented with abdominal swelling, one of whom was noted to have a mass the size of a 24-week pregnancy. Four of these seven had a palpable pelvic mass; four further patients who made no complaint of abdominal swelling also had a pelvic mass on examination. Five patients had some menstrual irregularity but only three presented primarily because of a menstrual problem. Three of these five were postmenopausal.

Complaints recorded as general symptoms (*Table 1*) included weight loss, lethargy and anorexia. These were most frequent in those patients with widespread malignancy. No patient complained of features of virilization.

Laparotomy was performed in all patients and the diagnosis made histologically. At initial operation eight individuals were found to have involvement of both ovaries. A ninth underwent a further laparotomy that revealed involvement of the other ovary. Ascites was present in nine cases, usually in large amounts; the greatest recorded volume was 4 litres.

The most common sites for primary tumours were the stomach and colon (*Table 2*). Of the ten individuals in whom the site of the primary was eventually determined, four were known to have tumours before they presented with ovarian metastases. The mean interval between diagnosis of the primary and evidence of metastases was 28 months. In two patients the primary and metastatic tumours were discovered at the same laparotomy and three others had primary tumours discovered within 5 weeks of the ovarian tumour. One patient presented with a Krukenberg tumour of the right ovary and multiple peritoneal metastases; no primary was identified and she died 5 years later. At autopsy no other malignancies were found, thus fulfilling the criteria for a primary Krukenberg tumour[10]. Microscopically all the tumours were of the classical type, where single signet cells predominate over lumen-forming cells[11,12].

Six patients were treated by pelvic clearance, the remainder undergoing unilateral or bilateral salpingo-oöphorectomy. One individual treated by unilateral salpingo-oöphorectomy subsequently had the other ovary excised at laparotomy 6 months later, by which time it was 13 cm in diameter. Six patients received chemotherapy. All patients survived the immediate postoperative period.

The mean survival time from diagnosis was 20·3 (range 1–>60) months. Three patients lived at least 5 years after diagnosis.

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Table 1 *Primary and associated complaints at presentation*

Patient no.	Age (years)	Abdominal pain	Abdominal swelling	Irregular menses	General symptoms
1	47	Primary	Primary		Primary
2	61	Primary	Associated		Associated
3	39		Primary	Associated	
4	67	Primary		Primary	Associated
5	56				Primary
6	57	Primary	Primary	Associated	Associated
7	37	Primary			Associated
8	49	Primary		Primary	Associated
9	44	Primary	Primary		Associated
10	46	Associated			Primary
11	73				Primary
12	47			Primary	
13	47	Primary			
14	45	Primary	Primary		Primary
15	39	Primary	Primary		

Table 2 *Timing of diagnosis of Krukenberg tumour related to survival*

		Time of diagnosis of primary			
Patient no.	Site of primary tumour	Before Krukenberg	At time of Krukenberg	After Krukenberg	Survival time (months)
1	Unknown				2
2	Breast			+	11
3	Unknown				15
4	Stomach	+			20
5	Unknown				9
6	Unknown				3
7	Stomach	+			>60*
8	Unknown				1
9	Colon		+		18
10	Colon		+		>60*
11	Stomach			+	3
12	Ovary		+		60
13	Stomach			+	2
14	Colon	+			20
15	Stomach	+			21

*Alive at time of writing

Discussion

The Krukenberg tumour is a rare metastatic ovarian cancer, the incidence of which has been reported by others using the criteria of Novak and Gray[6]. Soloway *et al.*[13] reported that approximately 5 per cent of all ovarian tumours were of the Krukenberg type. In the Woodruff and Novak[7] series of 1700 ovarian tumours, 48 fulfilled the criteria, representing 2·8 per cent of all ovarian malignancies on file at that time. These represented 28·8 per cent of all metastases to the ovary.

The mean age of the 15 patients in the present series (50·3 years) is slightly greater than in several previously reported[6,11–14] where the mean ages ranged from 42 to 47 years. Previous reports[13–15] suggest that abdominal pain and swelling are the most common presenting complaints, menstrual abnormalities being less frequent. Of 27 patients presented by Holtz and Hart[14], only three had menstrual irregularities. In this series, five patients had menstrual irregularities, greater than the proportion in the series of Holtz and Hart[14] but similar to the 36 per cent reported by Hale[8].

Ascites was present in nine patients, usually in considerable amounts. This incidence is slightly higher than in other series, which report 40–50 per cent of patients as having the condition[3,11,13]. Ascites in the present series was associated with a poor prognosis: a mean of 15·5 months compared with 30·0 months in patients with no ascites. There was a close association between bilateral tumour and ascites, which was present in eight of the ten patients with both ovaries affected.

Krukenberg tumours usually represent metastases from the stomach. Most series report that, where a primary source has been identified, this is the stomach in 60–70 per cent of cases[3,11,12,14,15]. The second most common site for a primary is the colon, found in 15–18 per cent of cases[11,12,14,16]. Only Israel *et al.*[17] reported more primaries in the colon than in the stomach. Other primary sites include breast and appendix[3,15,18–20]. Of the ten patients in the present series in whom a primary source was identified, five tumours were in the stomach. Of the five patients where the primary site was unknown, three were unfit for further investigation and died within a few weeks of diagnosis. The remaining two patients died within 15 months and no autopsy was performed.

The infrequency of ovarian malignancies that could be designated primary Krukenberg tumours suggests that all should be considered metastatic until proven otherwise. Should laparotomy prove inconclusive as to the source of the ovarian pathology, some suggest that further intensive investigation is required to identify a primary tumour[14].

The patients in this series who had primaries identified and underwent operation before or at the time of discovery of their Krukenberg tumour died a mean of 27·8 months from diagnosis (*Table 2*). There were, however, two patients from this group who were still alive at the time of writing, thus increasing the mean survival to at least 37·1 months. The mean survival time in those who had primaries discovered after their Krukenberg tumour was 5·3 months and where the primary site remained unknown the mean survival time was 6·0 months. Although the total number of patients within each of these groups is small, these figures suggest that patients in whom a primary is diagnosed before or at the time of the diagnosis of the Krukenberg tumour have the best prognosis, and that identification of a primary after removal of the ovaries makes little difference to the overall prognosis. In the absence of specific symptoms, it is unnecessary to embark on extensive investigations, which are unlikely to improve the patients' life expectancy and which further utilize already limited resources.

The population served by the pathology departments of the two hospitals during the study was 1·28 million (1981 census figures), of which 49·9 per cent were female. The incidence of the tumour in Northern Ireland is therefore 0·16 per 100 000 per annum. This is a rare condition that surgeons will encounter infrequently.

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Case report

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Enterolithiasis caused by a suture

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Stones rarely form in the gastrointestinal as opposed to the urinary and biliary tracts. They are usually expelled by gut peristalsis before they reach appreciable size. Relative stasis occurs in a number of conditions, notably stricture and diverticula, and predisposes to precipitation of various dissolved salts. Most radio-opaque enteroliths are detected incidentally and present a diagnostic challenge. They have been associated with haemorrhage, perforation, abscess formation and obstruction. An unusual cause of enterolithiasis is described that has not previously been reported. A polypropylene (Prolene; Ethicon, Edinburgh, UK) suture, which was accidentally passed through the jejunal wall after an incisional hernia repair, provided a static nidus. The enterolith that formed was discovered fortuitously and was initially misdiagnosed.

Case report

A 54-year-old man underwent laparotomy through a midline incision for generalized peritonitis secondary to perforated appendicitis. He developed an incisional hernia which was repaired 4 years later. Following this there was an intermittent discharge of purulent fluid from the wound, which had remained painful.

Some 6 years later the hernia recurred, with surrounding cellulitis. This region was explored, pus was drained and a Prolene suture was removed. A sinus track then formed and further Prolene suture material was removed.

A high-output enterocutaneous fistula developed. Fistulography showed a communication with the proximal jejunum. In an adjacent loop of jejunum distal to the fistula, a 1·6-cm filling defect was noted and was thought to represent a polyp (*Figure 1a*).

At laparotomy, two separate fistulas were identified between the skin and jejunum. A Prolene suture passed along one fistula to enter the jejunal lumen, at which point an enterolith was identified. Division of the suture allowed its removal with the enterolith attached to one end (*Figure 1b*). The segment of jejunum containing the fistulas was excised, an end-to-end anastomosis was fashioned and the recurrent incisional hernia was repaired. Biochemical analysis showed the enterolith to contain calcium, oxalate and urate.

Discussion

Enteroliths form in areas of stasis in the gastrointestinal tract. Dissolved salts often precipitate around a nidus such as a fruit seed. Their composition depends on the site of formation[1]. The relative acidity of the jejunum encourages precipitation of bile salts, which form radiolucent stones. The higher pH more distally favours precipitation of calcium salts, and these calculi tend to be radio-opaque.

Relative stasis occurs in a number of conditions. Acquired duodenal diverticula are seen in about 5 per cent of barium studies[2]. Congenital diverticula can occur anywhere; Meckel's diverticula are the most common, occurring in 1–4 per cent of people[2]. Bacterial overgrowth may be a further factor causing bile salts to deconjugate, thereby reducing their solubility[3].

Enteroliths proximal to strictures resulting from Crohn's disease, ulcerative colitis and tuberculosis have been reported. In one series of 400 patients with tubercular strictures, 3·2 per cent showed enterolithiasis[4]. An enterolith proximal to a congenital mucosal diaphragm has been reported[5].

Enteroliths may present incidentally or with obstruction, perforation or bleeding[3,4]. This case is unusual in that a suture was the nidus and the usual bowel stasis was not present. The correct diagnosis was made only at operation.

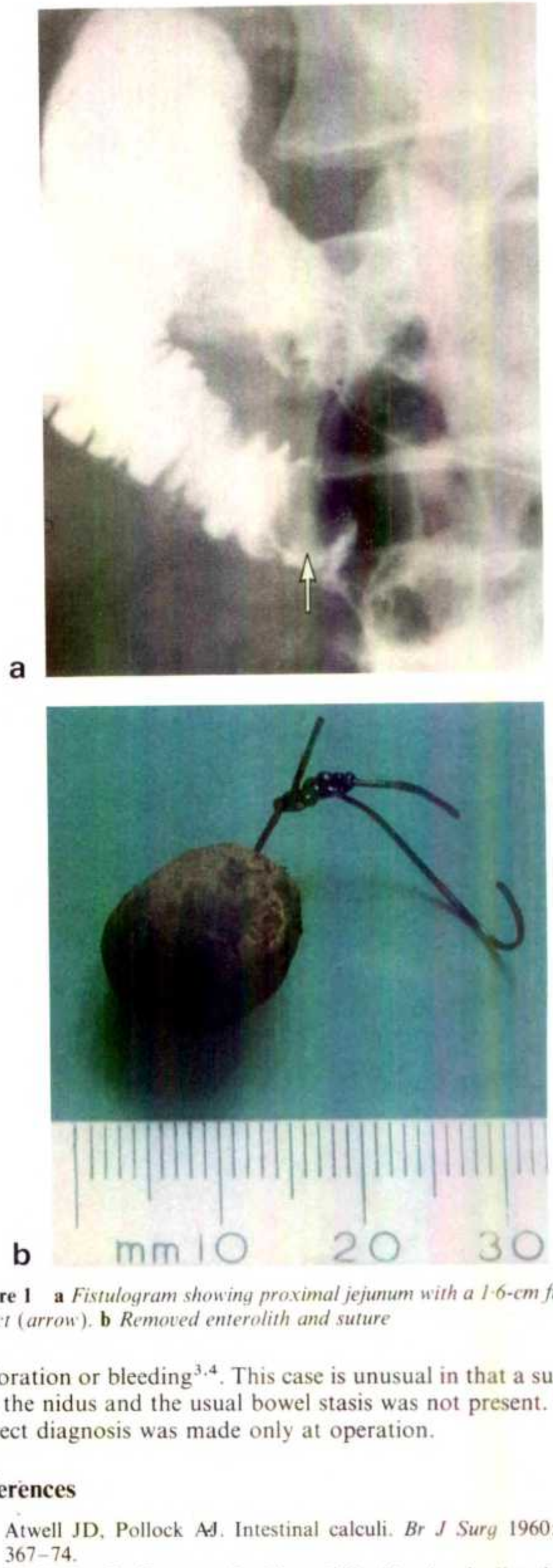

Figure 1 **a** *Fistulogram showing proximal jejunum with a 1·6-cm filling defect (arrow).* **b** *Removed enterolith and suture*

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Surgical workshop

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Laparoscopy via an indwelling cannula: an alternative to planned relaparotomy

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Planned re-exploration is advocated for peritonitis and ischaemic bowel necrosis[1–4] to confirm viability of the gut and to cleanse the abdominal cavity by irrigation and debridement. Both these objectives can now be achieved laparoscopically[5]. The aim of this study was to test whether a laparoscopic cannula left in the abdominal wall at the end of laparotomy for peritonitis or bowel necrosis is a useful tool to facilitate atraumatic and quick re-exploration. Insertion of the cannula at the primary laparotomy was thought likely to obviate the risk of bowel injury by blind insertion at the time of laparoscopy.

Surgical technique

Since January 1990, six patients with peritonitis or bowel necrosis have undergone laparoscopic re-exploration within 96 h of the primary laparotomy. In each case, a disposable cannula of diameter 12 mm and length 15 cm (Auto Suture, Tönisvorst, Germany) was implanted at the end of the laparotomy. The cannula was placed opposite the main region of interest; for instance, in the case of an abscess or anastomosis in the left upper quadrant, it was inserted in the right lower quadrant to provide an optimal view of the operative field. The cannula was inserted via a stab incision to the peritoneum. The internal end was drawn out of the abdomen via an additional peritoneal incision and snugly 'parked' in a pocket of the rectus muscle to avoid injury to the abdominal viscera (*Figure 1*). The head of the cannula was sutured to the skin.

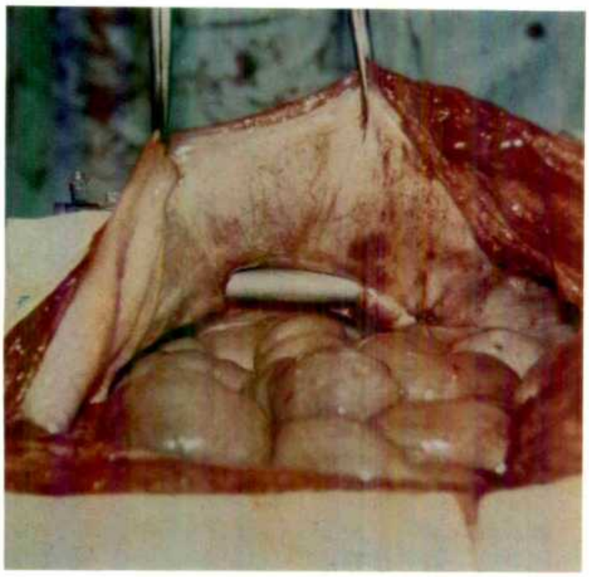

Figure 1 *Position of the cannula in the abdominal wall at the end of the primary laparotomy. The cannula is drawn through the abdominal wall and 'parked' in a pocket of the rectus muscle*

On laparoscopic re-exploration, the suture was removed, the cannula withdrawn 5 cm to release it from its muscle pocket, and the abdomen insufflated to 15 mmHg. Additional cannulas were inserted if necessary. Inspection, assessment of the gut and irrigation were performed. If further re-exploration was required, the cannula was again placed in the muscle pocket to allow subsequent laparoscopy. After the final laparoscopy, the cannula was removed and the skin closed.

Results

In three patients with abscess or mesenteric ischaemia, no further open re-exploration was necessary. The abdominal cavity was inspected and cleaned via the laparoscope. The incisions healed well and no hernia was observed.

In the other three patients, laparoscopic inspection indicated the need for open re-exploration, although irrigation and debridement were possible via the cannula. All three patients ultimately died from multiple organ failure.

Discussion

This series shows that laparoscopy via an implanted cannula 96 h after laparotomy is feasible. No incisional hernia has arisen to date, indicating that insufflation was well tolerated by the abdominal wall. No survivor needed relaparotomy. In patients who require a short re-exploration for confirmation of viability and exclusion of abscess, an implanted disposable laparoscopic cannula may be of use.

However, in the severely ill patients who developed necrosis of the abdominal wall requiring laparostomy, and who subsequently died from multiple organ failure, no benefit from laparoscopy could be demonstrated. Nevertheless, in these severe intra-abdominal infections, laparoscopic re-exploration via an implanted cannula may become an option. Such re-evaluation may offer some benefit by reducing morbidity in seriously ill patients. This approach deserves comparison by a randomized trial with planned relaparotomy[1,2] and laparostomy[4].

Pain was a problem in conscious patients, because movement was restricted and the device was disturbing. Local anaesthetic injection may be helpful. The current laparoscopic cannula is bulky and a more flexible device is required to facilitate endoscopic re-exploration.

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Psychological screening for non-specific abdominal pain

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Non-specific abdominal pain (NSAP) may have a detectable psychological component that could be used to predict outcome. To test this hypothesis, 131 patients aged 14–40 years admitted with acute abdominal pain were assessed using the General Health Questionnaire (GHQ) and Hospital Anxiety and Depression (HAD) scale, and a structured interview. Of 61 patients with NSAP, more had a psychosocial problem identified by the admitting registrar ($P < 0.01$) *and marginally more had high questionnaire scores. The risk of having NSAP was high if an abnormality on interview accompanied high questionnaire scores (relative risk 1·93 (95 per cent confidence interval (c.i.) 1·35–2·77)) or if prodromal pain had lasted >7 days (relative risk 2·13 (95 per cent c.i. 1·55–2·92)). After 2 years, patients with continuing pain had higher HAD and Spielberger Anxiety Trait scores (both* $P < 0.02$*); NSAP was associated with persisting pain (relative risk 2·22 (95 per cent c.i. 1·10–4·48)). Psychosocial factors are implicated in NSAP and in chronic pain, but the sensitivity and specificity of questionnaire assessment are too low to be useful in diagnosis.*

Of patients admitted with acute abdominal pain, 45 per cent will remain undiagnosed[1]. This is a significant burden on surgical resources. The term non-specific abdominal pain (NSAP) is frequently applied, although no common pathology has been demonstrated. Gray and Collin concluded that one possible cause might be a psychological component in patients with otherwise benign self-limiting conditions[1] No psychological pathology has, however, been identified and in the only prospective study to date (in which questionnaires were the sole assessment tool) the findings were negative[2] A prospective study with long-term follow-up was therefore conducted to determine whether structured psychological interviews or questionnaires could predict outcome.

Patients and methods

A total of 131 consecutive patients aged 14–40 years were admitted with abdominal pain to one surgical firm between October 1987 and December 1988. They were asked to complete two psychological questionnaires, the 30-item General Health Questionnaire (GHQ)[3] and the Hospital Anxiety and Depression (HAD) assessment[4]. These are global psychological measures designed to detect people at high risk of having psychiatric illness. After completion, the forms were filed unseen. In a structured interview enquiring about recent marital troubles, life events or other emotional problems, the admitting surgical registrar recorded the duration of symptoms, the preliminary diagnosis and whether an underlying psychosocial complication was suspected. The process of surgical management continued normally and diagnosis at discharge was recorded. Questionnaires were readministered to patients who attended the outpatient clinic after a median of 2 months The hospital records of all patients were examined after 1 year for details of histology, clinical course and reattendance. A final diagnosis of NSAP was accepted if subsequent outpatient attendance or investigation had resulted in a discharge from clinic without a specific diagnosis. At a median of 2 years, all 131 patients were contacted by post to complete further identical questionnaires and to establish whether symptoms had continued. The Spielberger Anxiety Trait questionnaire was administered at this point[5].

Scoring

After first follow-up, each admission questionnaire was scored. Each comprised a series of questions (items) with four alternative replies to be chosen by the patient according to the severity with which that particular item was perceived. The replies were allocated a number (1–4 in the HAD and Spielberger tests; 0 or 1 in the GHQ) and the numbers added to produce the global score. The HAD questionnaire was divided into a depression and an anxiety component and the GHQ could be subdivided into separate domains if desired A high score was defined by a total score >10 for either the anxiety or depression component of the HAD test and >5 for the GHQ[3,4]. The Spielberger questionnaire scores at 2 years were compared using a threshold of >44·5, the mean score found in general medical and surgical patients with psychiatric complications[5]. These thresholds were used to identify patients at risk of having a psychiatric problem. For all questionnaires and for the registrar's assessment, the numbers of high and low scorers between the groups with specific abdominal pain and NSAP were compared at each stage using the χ^2 test. The scores of 63 patients who completed follow-up questionnaires and 68 who filled in postal questionnaires were compared with the respective admission scores using Wilcoxon's paired rank test The responses concerning continued abdominal pain were compared using χ^2.

Results

Missing data

Patients were excluded from analysis only for the specific question or questionnaire on which data were missing. On admission, all patients completed the HAD questionnaire correctly, but eight (two with NSAP) failed to complete the second page of the GHQ. In nine patients the record of the admitting registrar's psychosocial assessment was incomplete, as was the case for the admission diagnosis in 14. At 2 months, 63 patients were asked to complete the GHQ and HAD test, but four and one respectively failed to do so correctly. At 2 years, 68 patients (52 per cent) replied to the postal questionnaire. Two patients each with NSAP and specific abdominal pain failed to answer the questions about further pain.

Diagnoses

The final diagnoses and the sex distribution are shown in *Table 1*. The NSAP group included five patients whose diagnosis was unconfirmed beyond hospital discharge. There were 36 operations; of 33 appendicectomies, histological examination confirmed the diagnosis of appendicitis in 24. Normal appendices were removed from three patients with no demonstrable pathology. The remaining six patients had a Meckel's diverticulum, pelvic inflammatory disease, enteritis, ruptured fimbrial cyst, cholecystitis and one had a pinworm infection which, in the absence of acute inflammation, was

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classified in the NSAP group. Two patients with the diagnosis of NSAP had normal appendices removed at a later date.

Scores on admission and at follow-up

The percentage of patients with NSAP and specific pain having a high score or psychosocial problem at each stage are shown in *Figure 1*. After interview, 38 patients were thought to have a psychosocial problem 24 of 55 (44 per cent) with an eventual final diagnosis of NSAP and 14 of 67 (21 per cent) with specific abdominal pain ($\chi^2 = 7{\cdot}28$, 1 d.f., $P < 0{\cdot}01$). Comparison of the admission and follow-up scores failed to demonstrate a significant change for patients in the specific pain or NSAP groups at 2 months or 2 years. Few patients had high scores in the depression component of the HAD questionnaire at any stage Of the nine patients who had a non-inflamed appendix removed, including the four with NSAP, eight had normal questionnaire scores on admission. The number of high questionnaire scores was similar in male and female patients: 24 and 20 per cent respectively for the HAD test, 45 and 39 per cent respectively for the GHQ. A psychosocial problem was diagnosed in 24 per cent of male and 34 per cent of female patients, but this difference was not statistically significant

Table 1 *Sex distribution in each diagnostic group and in those undergoing unnecessary appendicectomy*

	No	M	F
Diagnosis			
NSAP	61	22 (44)	39 (48)
Appendicitis	24	13 (26)	11 (14)
Pancreatitis	5	1 (2)	4 (5)
Gynaecological disorder	8	0 (0)	8 (10)
Upper gastrointestinal disorder	16	8 (16)	8 (10)
Renal colic or urinary tract infection	10	3 (6)	7 (9)
Miscellaneous	7	3 (6)	4 (5)
Total	131	50 (100)	81 (100)
Appendicectomy			
NSAP	4	1 (2)	3 (4)
Other diagnosis	5	2 (4)	3 (4)

Values in parentheses are percentages NSAP, non-specific abdominal pain

Assessment of admission data as screening tools

The risk of a diagnosis of NSAP was calculated for all the variables recorded on admission The relative risks, sensitivities and specificities are shown in *Table 2*. In the 117 patients with a recorded admission diagnosis, the initial diagnosis of NSAP was the single factor most strongly associated with a subsequent final diagnosis of NSAP The registrar's diagnosis of a psychosocial problem was also significantly associated with a final diagnosis of NSAP. A high score in the HAD questionnaire and GHQ, alone or combined, was not. A diagnosis of NSAP on admission was not associated with a diagnosed psychosocial problem (odds ratio 1·39 (95 per cent confidence interval (c.i.) 0·62–3·14)) and there was no significant association between the diagnosis of a psychosocial problem and the HAD or GHQ scores (odds ratio (95 per cent c.i.) 2·31 (0·95–5·64) for the HAD test, 1·82 (0·82–4·05) for the GHQ).

Of 11 patients with high scores in both questionnaires also deemed to have a psychosocial problem on interview, nine had NSAP (relative risk 1·93 (95 per cent c.i. 1·35–2·77)). Of nine patients with symptoms lasting >1 week before admission, eight had NSAP (relative risk 2·13 (95 per cent c.i. 1·55–2·92)). No test or combination of tests had a sensitivity >50 per cent.

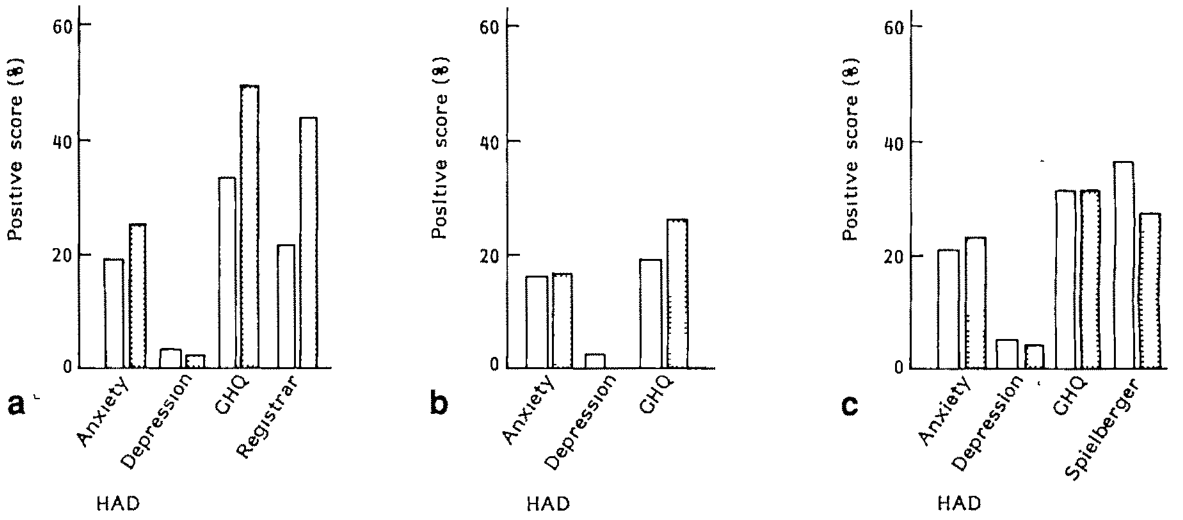

Figure 1 *Positive scores for patients with specific* (☐) *and non-specific* (▨) *abdominal pain in different tests* **a** *on admission*, **b** *after 2 months and* **c** *after 2 years. HAD, Hospital Anxiety and Depression, GHQ, General Health Questionnaire*

Table 2 *Recordings on admission as screening tools for non-specific abdominal pain*

	HAD score	GHQ score	Psychosocial problem	Initial diagnosis NSAP	Pain for >7 days	HAD and GHQ scores	HAD and GHQ scores and psychosocial problem
Sensitivity (%)	26	49	44	47	15	24	21
Specificity (%)	81	67	79	86	99	86	97
Relative risk (95% c.i.)	1·25 (0·84–1·85)	1·41 (0·98–2·03)	1·71 (1·18–2·48)	3·49 (1·80–6·77)	2·13 (1·55–2·92)	1·35 (0·91–2·00)	1·93 (1·35–2·77)

HAD, Hospital Anxiety and Depression, GHQ, General Health Questionnaire, NSAP, non-specific abdominal pain, c.i., confidence interval

Table 3 *Factors associated with continuing pain at 2 years*

		Admission			2 years		
	NSAP	HAD score	GHQ score	Psychosocial problem	HAD score	GHQ score	Spielberger score
Pain ($n = 21$)	12	5	11	10 of 19	9	9	11
No pain ($n = 43$)	12	4	13	5 of 40	6	11	9
Relative risk (95% c.i.)	2·22 (1·10–4·48)	1·91 (0·93–3·91)	1·83 (0·92–3·66)	3·26 (1·64–6·46)	2·45 (1·29–4·66)	1·65 (0·83–3·27)	2·42 (1·23–4·75)

NSAP, non-specific abdominal pain, HAD, Hospital Anxiety and Depression; GHQ, General Health Questionnaire; c.i., confidence interval

Assessment of outcome at 2 years

In the 2-year postal questionnaire, in answer to the question 'Do you still suffer from the pain that caused your first admission to hospital?', 21 patients gave positive and 43 negative replies. A significant difference in Anxiety Trait emerged between the two groups In *Table 3*, the risk of having continuing pain is compared for each of the variables recorded on admission and at 2 years. Those with continuing pain included more with a psychosocial problem diagnosed on admission ($\chi^2 = 10{\cdot}94$, 1 d.f., $P < 0{\cdot}001$), a final diagnosis of NSAP ($\chi^2 = 5{\cdot}15$, 1 d.f., $P < 0{\cdot}05$), and at 2 years a high HAD ($\chi^2 = 6{\cdot}57$, 1 d.f., $P < 0{\cdot}02$) and Spielberger ($\chi^2 = 6{\cdot}50$, 1 d.f., $P < 0{\cdot}02$) score.

Discussion

Many organic causes of NSAP have been suggested[1]. Attempts at diagnosis and treatment must consume a significant amount of surgical resource. In this study, 47 per cent of patients had NSAP, close to the overall rate of 43 per cent reported in two large studies[6,7], in one of which a rate of 51 per cent was noted in patients aged 10–29 years. Because psychosocial aspects are seldom addressed routinely, a genuine psychological or social problem may be overlooked. Previous studies have shown that patients who had normal appendices removed were emotionally distressed[8,9] or had an increased incidence of adverse life events[10]. In the only prospective study, low scores were reported in patients with NSAP and controls alike[2]. A preponderance of NSAP in female patients who scored higher for anxiety and abnormal illness behaviour has been reported[11], but NSAP and higher psychological scores were not more common in women in this study.

A preliminary diagnosis of NSAP was the best predictor of a final diagnosis of NSAP. The registrar's diagnosis of a psychosocial problem was better than the HAD questionnaire or GHQ, but a positive bias may have occurred where a surgical diagnosis was uncertain. A preliminary diagnosis of NSAP and a psychosocial problem were not significantly associated. Using a positive score in both the GHQ and the HAD test, ten patients of 25 would have been wrongly diagnosed as having NSAP, including three with appendicitis and two with pancreatitis. The combination of psychosocial assessment, HAD questionnaire and GHQ identified a small but specific group at high risk of having NSAP, but similar specificity was obtained using a cut-off of >7 days of prodromal pain. The simple measure of recording a 'closed eyes sign' on abdominal palpation had a predictive value of 79 per cent for NSAP[12] and computed-aided diagnosis may reduce unnecessary admissions by 25 per cent[13]. Computer-aided diagnosis has not been widely adopted and any approach needing extensive data collation may not be attractive for clinical implementation.

Higher HAD anxiety and Spielberger trait scores were found in patients with persistent pain at 2 years, but volunteer bias cannot be discounted since the compliance rate was low despite repeated postal and telephone follow-up. The registrar's psychosocial diagnosis was the closest predictor of persistent pain but it is unclear whether psychosocial factors or pain come first. Similar uncertainty was seen in a study of the irritable bowel syndrome in which patients with bowel dysfunction had higher HAD scores than controls[14].

An adverse psychosocial history with positive questionnaire results identifies a small group of patients at high risk of having NSAP, but it remains easier to admit all patients with acute abdominal pain than to diagnose NSAP.

Acknowledgements

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Rectal cancer risk in patients treated for familial adenomatous polyposis

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Total colectomy with ileorectal anastomosis (IRA) in familial adenomatous polyposis (FAP) leaves patients at risk for rectal cancer. To assess this risk, the rectal cancer incidence in 297 patients with FAP undergoing IRA since 1951 was determined in the population-based registers of Denmark, Finland and Sweden. At the same time, detailed data on 50 patients with FAP and invasive rectal cancer were obtained from 11 international polyposis registries. The cumulative incidence of rectal cancer was 13·1 per cent at 25 years. The 5-year survival rate of patients with FAP developing rectal cancer was 71 per cent. Combining both studies, the risk of dying from rectal cancer after IRA was 2·0 per cent at 15 years of follow-up. These results justify IRA as primary treatment for most patients; restorative proctocolectomy is preferred for some subgroups. The high all-cause mortality rate observed in this relatively young population necessitates lifelong surveillance of patients with FAP.

Two treatment options are currently available for patients newly diagnosed with familial adenomatous polyposis (FAP) without cancer of the middle or distal rectum: total colectomy with ileorectal anastomosis (IRA) or restorative total proctocolectomy with ileoanal reservoir (RPC). Preservation of the rectum probably affords a superior quality of life but leaves the patient at risk of rectal cancer and its consequences. The extent of these risks is controversial.

At the Mayo Clinic[1], 46 of 143 patients with FAP (32·2 per cent) developed cancer in the retained rectum during a median follow-up of 17·5 years. In a population-based study in Denmark[2], the cumulative risk of rectal cancer at 5 and 10 years after IRA was 3·5 and 13·3 per cent respectively. In 174 patients who had undergone IRA at St Mark's Hospital, London[3], the cumulative risk of rectal cancer rose to 13 per cent at 25 years. At the Cleveland Clinic[4], ten of 133 patients (7·5 per cent) at risk developed rectal cancer during a median follow-up of 5·5 years, ranging up to 37 years.

The mortality risk of rectal cancer after IRA has been difficult to examine systematically. In a group of seven patients with rectal cancer, five survived long term[5]. At St Mark's Hospital, 12 patients had rectal cancer, resulting in four deaths[6]. Mortality risks from causes other than colorectal cancer have been published[3,7,8].

In 1991 the Leeds Castle Polyposis Group initiated a two-part study of long-term treatment outcomes in patients with FAP. In one arm of the study, population-based registries in Denmark, Finland and Sweden assessed 297 patients who had undergone IRA over a 40-year period for long-term risk of rectal cancer. In the other arm, data on clinical findings and long-term results of invasive rectal cancer in 50 patients after IRA were collected from 11 polyposis registries in seven countries.

Patients and methods

The Scandinavian study participants were 297 patients who had undergone total colectomy and IRA for FAP and were followed for at least 1 year before 1991. The patients were identified through the national registers of Denmark (88 patients), Finland (90) and Sweden (119). These patients were unselected over a 40-year span from the entire population of these nations; accession is believed to be virtually complete. Basic demographic and clinical data were collected and analysed for each patient; privacy was protected. Survival functions and risk of rectal cancer were determined by BMDP Statistical Software (BMDP, Los Angeles, California, USA) according to actuarial methods[9].

In the registry study, 11 member registries in the Leeds Castle Polyposis Group submitted data on all patients with FAP who had undergone IRA and were diagnosed before mid-1986 with invasive rectal cancer in the retained rectum. The registries applied uniform standards for basic clinical determinants, tumour staging and follow-up. Only patients for whom a minimum of 5 years of follow-up was available were included. Patients with *in situ* rectal cancer were excluded; privacy was protected. Data were entered into an Epi Info database (USD, Stone Mountain, Georgia, USA)[10]. Analyses were performed on continuous data by Student's t test and on categorical data by the χ^2 test or, where appropriate, Fisher's exact test. Survival data were analysed with the Lifetest procedure (SAS Institute, Cary, North Carolina, USA)[11]. Five patients with rectal cancer and 135 who had undergone IRA were common to the Scandinavian and registry components.

Results

Scandinavian study

The median age of the 297 patients at IRA was 27 (range 10–77) years. Thirty-four patients were $\geqslant 50$ years of age at the time of IRA. There were 145 male and 152 female patients. Of the 297 patients, 102 were probands with a median age of 36 (range 12–77) years and 195 were call-up patients with a median age of 24 (range 11–63) years.

Thirty-five of the 297 patients (11·8 per cent) had colonic cancer, three (1·0 per cent) rectal cancer found within 1 year of IRA and regarded as a prevalent cancer, and 13 (4·4 per cent) subsequently developed rectal cancer. Fourteen patients were lost to follow-up.

For the 259 patients without colonic cancer, the median age at IRA was 25 (range 11–77) years and survival rates were 97·1 per cent at 5 years, 92·5 per cent at 10 years, 88·8 per cent at 15 years and 88·8 per cent at 20 years, by which time 42 patients remained at risk. For the 35 patients with colonic cancer, the median age at IRA was 44 (range 23–68) years and survival rates were 72·9 per cent at 5 years, 63·8 per cent at 10 years and 55·8 per cent at 15 years, seven patients remaining at risk by this time.

During follow-up after IRA, the remaining rectal segment was removed for non-malignant causes (multiple large polyps,

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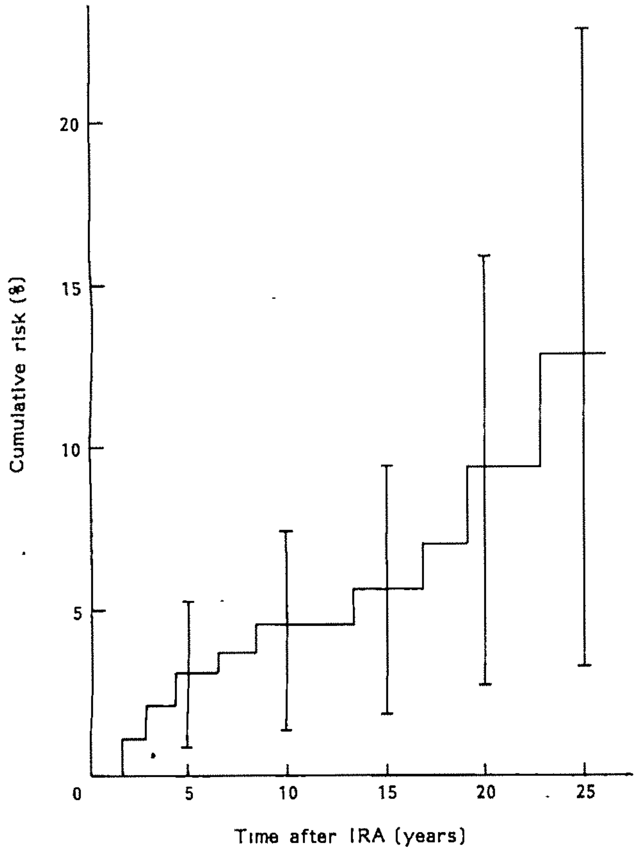

Figure 1 *Cumulative probability of rectal cancer after ileorectal anastomosis (IRA) over 25 years of follow-up among patients in the Scandinavian study. Bars are 95 per cent confidence intervals*

severe dysplasia) in 34 patients. The cumulative probability of excision of the remaining rectum for causes other than carcinoma was 4·4 per cent at 5 years, 9·4 per cent at 10 years, 14·4 per cent at 15 years, 17·4 per cent at 20 years and 30·9 per cent at 25 years.

The cumulative risk of rectal cancer (*Figure 1*) after IRA in the 294 patients without rectal cancer was 3·1 per cent at 5 years, 4·5 per cent at 10 years, 5·7 per cent at 15 years, 9·4 per cent at 20 years and 13·1 per cent at 25 years; 21 patients remained at risk. Of the 13 patients who developed rectal cancer, four died from metastatic disease. Sex and the presence of colonic cancer at the time of IRA did not affect the risk of subsequently developing rectal carcinoma. Inclusion in risk calculation of the three patients diagnosed with rectal cancer within 1 year of IRA did not change these estimates substantially: the cumulative risk was 10·5 per cent at 20 years and 14·2 per cent at 25 years.

The effect of age on risk for rectal cancer was examined. The cumulative probability of developing rectal cancer by age 50 years was 5·2 per cent (95 per cent confidence interval 1·2–9·2 per cent). By 60 years this figure was 14·1 per cent (95 per cent confidence interval 4·1–24·1 per cent).

Registry study

From the 11 polyposis registries, 50 patients with invasive rectal cancer in the retained rectum were identified, constituting 3·7 per cent of 1363 registered patients who were at risk after IRA performed before mid-1986. The median age of these 50 study patients at IRA was 33 (range 10–60) years. There were 27 male and 23 female patients. Eleven of the 50 had an invasive colonic cancer at the time of IRA.

The median interval from IRA to the detection of invasive cancer was 11 (mean 13·4, range 0·1–36) years. The median interval was 13 years for women and 8 years for men ($P = 0{\cdot}29$). Four patients with rectal cancer were treated within 1 year of IRA and were regarded as having a prevalent cancer.

Determinants at detection of rectal cancer. The median age of the 50 patients at the detection of rectal cancer was 46 (mean 46, range 18–67) years. Lower gastrointestinal symptoms were present in 19 patients, absent in 19 and not known in 12. The interval from the most recent endoscopy to cancer detection was ≤ 6 months in 24 patients, 7–12 months in eight, 13–24 months in seven, >2 years in four and unknown in seven. In 37 cases, the previous endoscopy had been performed by a member of the participating polyposis centre or by another physician regarded as reliable. Subsequent Dukes' classification and survival were not affected by the presence of lower gastrointestinal symptoms and had little relationship to the interval from previous endoscopy. All four patients whose cancer was found >2 years after their last endoscopy had a Dukes' C lesion.

The 50 patients were segregated into quartiles between 1952 and mid-1986 by the date of detection of rectal cancer and the quartiles compared for distribution of Dukes' classification of the rectal tumour (unknown in three). More Dukes' A and fewer Dukes' C cancers were found in the most recent quartile (*Figure 2*) ($P = 0{\cdot}02$, Fisher's exact test).

The distance from the anal verge to the IRA was known in 40 patients; the median was 15·0 cm and the mean(s.d.) 14·3(4·3) cm. In 38 patients the distance from the anal verge to the distal edge of the rectal cancer was known. The median was 8·5 cm and the mean(s.d.) 7·5(3·6) cm. The maximum diameter of the rectal cancer was known in 40 patients; the median was 3·9 cm and the mean(s.d.) 3·3(1·7) cm.

The distances from the central point of the rectal tumour to the anal verge and IRA were determined in the 33 patients for whom all measurements were known (*Figure 3*). Of the 33 tumours, 18 occurred in the most cephalad third of the remaining rectum ($\chi^2 = 2{\cdot}21$, 1 d.f., $P = 0{\cdot}14$). These 33 patients included ten of 11 who had colonic cancer at the time of IRA. Of the ten, eight had a rectal tumour in the upper third of the rectal segment ($P = 0{\cdot}08$, Fisher's exact test). No tumours were reported in the most distal 4 cm of the rectum.

Of ten patients with a tumour <2 cm in diameter, only one died from rectal cancer. For larger tumours no correlation of size with survival was evident.

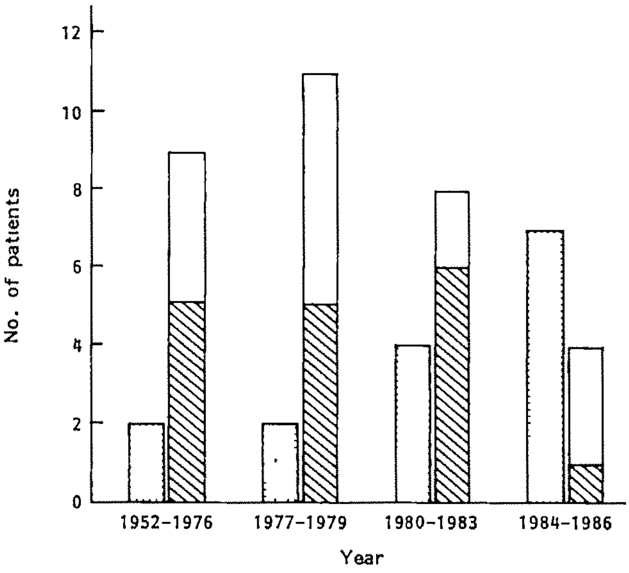

Figure 2 *Dukes' classification of invasive rectal cancer by year of diagnosis among patients in the registry study.* □, *Dukes' A,* □, *Dukes' B and 'D' (disseminated),* ■, *Dukes' C Patients diagnosed in the latest quartile were more likely than those in earlier quartiles to have Dukes' A rectal cancers* ($P = 0{\cdot}02$, *Fisher's exact test*)

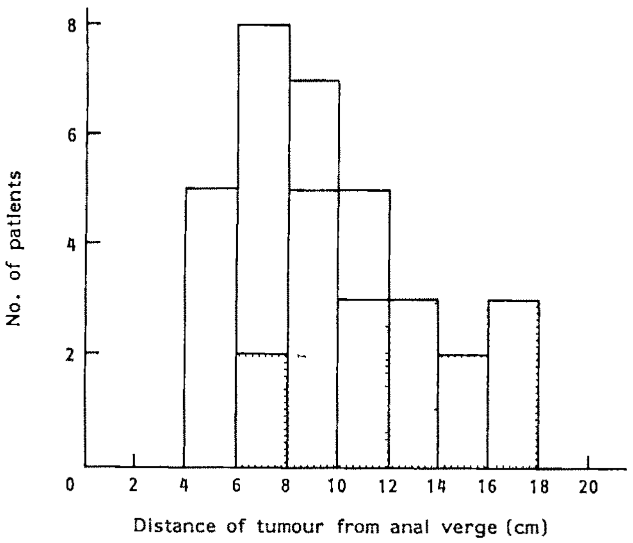

Figure 3 *Distance from the anal verge to midpoint of the rectal tumour in patients in the registry study.* ☐, *Tumours within the cephalad third of retained rectum*

Table 1 *Dukes' classification and mortality from rectal cancer by sex*

	M		F	
Dukes' classification	No	Deaths	No.	Deaths
A	8	0	7	2
B	5	2	7	1
C	11	7	6	0
Disseminated	3	3	0	0
Unknown	0	0	3	1
Total	27	12	23	4

Treatment. Of the 50 patients, 42 underwent abdominoperineal resection and six low anterior resection; one of the latter was treated palliatively. Two patients with disseminated cancer did not undergo surgery and two died after operation.

Results of treatment. Fifteen patients had a Dukes' A cancer, 12 Dukes' B and 17 Dukes' C. Three had disseminated cancer, and classification was unknown in three (*Table 1*). The overall all-cause 5-year survival rate was 66 per cent and the 10-year rate 36 per cent. The 5-year rectal cancer survival rate was 68 per cent, 56 per cent in men and 83 per cent in women ($P = 0{\cdot}04$, log rank test) (*Table 1*). Of the 11 men with a Dukes' C lesion, eight had full-thickness penetration of the primary tumour (Astler–Coller class C_2). Of the six women with regional lymph node involvement, three had full-thickness penetration of the primary tumour.

Excluding the three patients treated palliatively and the two who died after operation, the remaining 45 patients had an actual 5-year survival rate of 71 per cent. The 5-year survival rates were 77 per cent for the 15 patients with Dukes' A cancer, 75 per cent for the 12 with Dukes' B lesion and 62 per cent for the 17 with Dukes' C cancer. Of the 17 patients who died during the first 5-year interval, 14 died from rectal cancer and three after operation.

The actual 10-year survival rate in the 29 eligible patients was 55 per cent. During this second 5-year interval, six patients died: two from rectal cancer shortly after the 5-year mark and four from other causes. The 10-year rectal cancer survival rate for patients with Dukes' C lesions was 50 per cent.

Of the 13 patients surviving to 10 years, five have since died from conditions not related to colorectal cancer.

Discussion

This study has determined a cumulative risk for rectal cancer of 13·1 per cent (95 per cent confidence interval 3·3–22·9 per cent) at 25 years in the population-based Scandinavian data. This result is similar to the 13 per cent risk estimate at 25 years in a hospital-based registry[3].

If these estimates are combined with mortality rates from the registry study, the risk of dying from rectal cancer, given prior IRA with absence of colonic cancer, was 1·0 per cent (3·1 × 0·32) at 10 years and 2·0 per cent (4·5 × 0·45) at 15 years. This is a more favourable result than that of Bussey *et al.*[3]. These estimates do not consider the potential benefit of better surveillance and of nutritional modification and chemoprevention[12–14].

The present observations suggest that retention of the rectum may have less life-threatening consequences than generally believed, and support a general policy of IRA in primary operative management of patients with FAP[15]. RPC should be the primary procedure for those with middle or upper rectal tumours or with large or confluent adenomas of the rectum, and for those who will not subscribe to regular follow-up.

The Scandinavian study may provide a rationale for recommending RPC as the primary procedure in older patients. The benefit of this procedure must be weighed against an increased risk of morbidity at the primary operation and further deterioration during subsequent ageing. Of the 34 Scandinavian patients who underwent IRA at ≥50 years of age, only two subsequently developed rectal cancer. The course of FAP in older newly diagnosed patients may be relatively indolent, making a more extensive operation and attendant morbidity difficult to justify.

In the 50 registry patients, the distribution of rectal cancer by Dukes' classification approximated that observed in patients with sporadic colorectal cancer. Survival by Dukes' class, however, seemed superior, especially in women. This may be due to greater health awareness, especially among women, leading to more expeditious diagnosis and treatment and earlier substages of rectal cancer. The registry group included more men than women, and the former had shorter time intervals from IRA to rectal cancer, a greater likelihood of being diagnosed Dukes' C and Astler–Coller C_2 (these differences were not significant) and a higher mortality rate.

Evidence for the benefit of surveillance was mixed. Except for delay in follow-up endoscopy >2 years, the frequency of endoscopy made no difference in Dukes' classification at diagnosis or in survival, a finding previously noted[16]. Patients diagnosed since 1978 were more likely to have a Dukes' A tumour. This difference, if real, may be the product of improved health awareness in patients and alertness in physicians. These observations suggest that follow-up endoscopy should be performed at least every 6 months.

As in sporadic colorectal cancer[17] (except for rectal lesions <2 cm in diameter) tumour size was not correlated with survival. After discounting the epithelium between the anal verge and the dentate line, the most caudad few centimetres of rectal mucosa appeared spared from rectal cancer. This may be due to the presence of transitional, not columnar, epithelium in the most distal 1–2 cm of rectal mucosa[18]. This finding may support mucosal preservation during RPC.

Because rectal cancer appeared to occur more frequently in the upper third of the retained rectum, especially in those with colonic cancer at the time of IRA, a low IRA 10–12 cm from the anal verge is recommended[19].

This study does not address the full range of causes of mortality in this comparatively young patient population. Perioperative risks should have decreased over the 40-year span of this study but other genetically based risks have become more prominent[3,7,8]. In one registry of 174 patients with IRA, 35 died during follow-up, only seven of them from colorectal cancer[3]. Another study of 36 patients who died after IRA reported only three deaths from rectal cancer[8]. In both studies the most frequent causes of death were desmoid disease and periampullary cancer; these occurred in only 4 and 1 per cent respectively of patients of the Danish register[20].

During the 353 patient-years of follow-up represented by the registry study, 16 patients died from rectal cancer, 14 within the first 5 years. Twelve patients died from other causes: perioperative deaths (three), upper gastrointestinal cancer (four), suicide (two), desmoid disease (one), thermal trauma (one) and myocardial infarction (one). Nine of these deaths occurred after the 5-year mark These findings highlight the need for lifelong comprehensive monitoring of these patients. The suicides, noted by others[3,8], justify counselling for patients whose lives remain threatened by continuing risk of inherited disease.

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The authors dedicate this paper to H. J. R. Bussey (1907–1991).

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Intraoperative colonoscopy in patients with colorectal cancer

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Sixty-seven patients underwent intraoperative colonoscopy during elective surgery for colorectal cancer. Complete examination of the colon was achieved in 65 patients (97 per cent), albeit with insertion through a colotomy in three (4 per cent). A synchronous carcinoma was found in six patients (9 per cent), which necessitated a change of planned surgical procedure. Synchronous polyps were detected and removed in 24 patients (36 per cent); two had polyps with carcinoma in situ. *The mean age of patients with synchronous carcinoma was significantly higher than that of those without (74·1* versus *61·2 years,* P = *0·02). Intraoperative colonoscopy took a mean of 15 min surgical time and only two minor complications (serosal lacerations) were encountered. In patients with colorectal cancer, intraoperative colonoscopy allows complete assessment of the colon and identifies synchronous lesions.*

The incidence of synchronous lesions in patients with colorectal cancer varies from 2 to 11 per cent for carcinoma and from 27 to 60 per cent for adenoma[1–23]. The whole of the large bowel should therefore be assessed before surgery is performed in patients with colorectal cancer. Failure to detect synchronous carcinoma before operation may produce prognostic and therapeutic mistakes. Early metachronous carcinomas (diagnosed <3 years after surgery) may be missed synchronous lesions, patients with undetected synchronous carcinoma may undergo inappropriate surgical procedures[3,4,12–16,22].

The preoperative diagnosis of synchronous carcinomas is difficult[4,5,11,12,16,21] Fibreoptic colonoscopy is the most useful method, but it is often not possible to perform complete colonoscopy because of bowel stenosis[20,21,24–28]. Double-contrast barium examination detects between only 50 and 70 per cent of synchronous lesions and peroperative manual palpation of the large bowel misses almost half such tumours[8,11–13,21,26]

This study evaluated the efficacy of intraoperative colonoscopy for the detection of synchronous lesions during elective surgery in patients with colorectal cancer, and assessed its effect on the planned surgery.

Patients and methods

In 1988, a collaborative protocol for assessment of patients with colorectal cancer was developed. When a tumour of the large bowel was observed at colonoscopy, total colonoscopy was not attempted A barium enema examination was not performed before surgery and colonoscopy was arranged to be carried out during the elective operation

The bowel was cleansed with polyethylene glycol electrolyte lavage solution (3000 ml) given orally the day before surgery Antibiotic prophylaxis comprised one dose of metronidazole and gentamicin before surgery and two afterwards. The colonoscope was submerged in 2 per cent glutaraldehyde for 20 min before use The endoscopist and nurse took similar antiseptic precautions to other personnel in the operating theatre

The patient was placed in the Lloyd-Davies position After laparotomy and inspection of the abdominal cavity, the primary tumour was located and manual palpation of the entire colon carried out The terminal ileum was occluded with a non-crushing clamp to avoid intestinal distension from air insufflation during endoscopy The colonoscope was advanced through the colon under direct control of the surgeon, who facilitated its progression in the event of stenosing lesions or during pull-back manoeuvres. During withdrawal of the endoscope, air was aspirated while the surgeon examined the serosa to detect possible injury.

When stenosing neoplasms blocked the passage of the colonoscope, the instrument was cleaned and reintroduced via a colotomy at the proximal margin of the planned surgical resection A small colotomy (1 5 cm) enabled the colonoscope to pass but did not allow air to escape. Antiseptic measures were applied around the colotomy to prevent contamination during intraoperative colonoscopy

Endoscopic polypectomy was performed when polyps were located outside the planned surgical resection limits A synchronous carcinoma was defined by the criteria of Kaibara *et al.*[17]

Results

Between December 1988 and December 1990, intraoperative colonoscopy was performed in 67 patients with colorectal cancer (49 men and 18 women) with a mean(s.d) age of 63·5(12·8) years. None of the patients had a history of ulcerative colitis, familial adenomatous polyposis or previous surgery for colorectal cancer The location of the primary tumour was the rectum in 37 patients (55 per cent), the sigmoid colon in 21 (31 per cent), the descending colon in seven (10 per cent) and the transverse colon in two (3 per cent) The tumour was causing stenosis in 39 patients (58 per cent).

Full examination of the colon was achieved without help from the surgeon in 40 patients (60 per cent). Of the other 27 patients, the stenosis was negotiated after manipulation by the surgeon in 22 and the colonoscope could not be advanced in five. Full examination of the colon was achieved in three of these by reintroduction of the endoscope through a colotomy This procedure was not carried out in two patients who underwent palliative surgery owing to advanced age and multiple peritoneal metastases. Complete colonoscopy was thus accomplished in a total of 65 patients (97 per cent).

Intraoperative colonoscopy was normal in 37 patients (55 per cent) In 24 (36 per cent), polyps located outside the planned resection limits were detected and removed. In two patients the polyps contained carcinoma *in situ.*

Synchronous carcinoma was found in six patients (9 per cent) (*Table 1*) In five the primary tumour was located in the rectum and in four was stenosing. All six had associated adenomatous polyps. Only four synchronous tumours were detected by manual palpation during surgery; two were discovered by intraoperative colonoscopy. The planned surgical approach was modified in all cases.

The mean age of patients without synchronous lesions was 61·2 years and for those with synchronous polyps 65·3 years. Patients with synchronous carcinoma were significantly older

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Table 1 *Details of six patients with synchronous carcinoma*

			Primary tumour			Synchronous tumour			
Patient no.	Sex	Age (years)	Location	Stage*	Stenosis	Location	Stage*	Detection by manual palpation	Final surgical procedure†
1	F	79	Rectum	$T_2 N_2$	Yes	Splenic flexure	$T_2 N_1$	No	Enlarged resection
2	M	74	Rectum	$T_2 N_0$	Yes	Transverse colon	$T_3 N_1$	Yes	Enlarged resection
3	M	73	Rectum	$T_3 N_2$	Yes	Caecum	$T_2 N_1$	No	Enlarged resection
4	M	81	Rectum	$T_2 N_0$	No	Sigmoid colon	$T_4 N_3$	Yes	Palliative colostomy (peritoneal metastases)
5	M	69	Rectum	$T_2 N_0$	No	Sigmoid colon	$T_3 N_1$	Yes	Enlarged resection
6	F	69	Transverse colon	$T_4 N_2$	Yes	Caecum	$T_3 N_2$	Yes	Enlarged resection

*Tumour node metastasis classification. †The planned surgical approach was modified in all six cases

than those without (mean age 74·1 *versus* 61·2 years; $P = 0.02$, analysis of variance).

Serosal laceration was noted and repaired in two patients during surgery. In both, intraoperative colonoscopy was technically difficult because of adhesions and needed complex endoscopic manipulation and help from the surgeon. The mean duration of intraoperative colonoscopy was 15 min. If endoscopic polypectomy or surgical help was needed, the mean time was 21 min, it was 9 min when polypectomy or manual help were not required.

Discussion

Synchronous carcinoma is clinically important because of its incidence, the difficulty of preoperative diagnosis, and the therapeutic and prognostic implications of missed lesions[1,4–7,16,19,22,23]. The reported incidence[12–15] of synchronous carcinoma in patients with colorectal cancer ranges from 1·5 to 11 per cent; this variation may be due to factors such as the criteria used to define synchronous cancer, design of the study, and diagnostic methods employed. Diagnosis of synchronous lesions may be difficult because in many patients is not possible to perform full preoperative colonoscopy because of tumour stenosis[20–22,24,27]. In prospective studies, examination of the entire colon was achieved in only 42–60 per cent of cases and periodic postoperative colonoscopy was recommended to detect early metachronous carcinoma[19–21,26,29]. This policy can be challenged because the detection of a second tumour may determine a different resection.

The technique and utility of intraoperative colonoscopy has been documented[29–35] for localization of non-palpable colonic lesions, investigation of unexplained recurrent gastrointestinal haemorrhage, assessment of the extent of inflammatory bowel disease or when there is an inability to complete colonoscopy before operation. Intraoperative colonoscopy was selectively employed by Kaibara *et al.*[36] for the detection of synchronous lesions and was performed through a colotomy; they found an incidence for synchronous neoplasm of 8·6 per cent. Finan *et al.*[13] proposed the same strategy.

In the present study the incidences of synchronous carcinoma and large polyps with carcinoma *in situ* are similar to those of Kaibara using intraoperative colonoscopy[36]. Total examination of the large bowel was achieved in 97 per cent of patients, significantly higher than the yield in preoperative colonoscopy[20–27]. Polyps were observed in 36 per cent of patients, and those with synchronous lesions were older than those with a single carcinoma[6,8,11,13,15].

The prognosis of patients with synchronous carcinoma is not different from that of those with a single carcinoma[8,9,21], but preoperative detection of synchronous lesions allows a more appropriate surgical procedure[9,11,14,15,17,21,29]. In this study the intraoperative colonoscopy findings allowed the modification of the planned surgical approach in all patients with synchronous carcinoma.

Intraoperative colonoscopy is a useful method of achieving full examination of the colon and identifies synchronous lesions, notably in those patients with stenosing tumours[13,36]. It does not prolong operating time and complications are both minor and rare. Intraoperative colonoscopy allows a 'clearing' of the colon, removing polyps and preventing possible early metachronous carcinomas. The impact of intraoperative colonoscopy on survival in patients with colorectal cancer has to be determined.

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Anovaginal and rectovaginal fistula in patients with Crohn's disease

Between 1971 and 1991, details of 67 women with perianal Crohn's disease were recorded prospectively using the Cardiff classification. Two groups were identified according to the presence (n = *29*) *or absence* (n = *38*) *of anorectal Crohn's fistula involving the vagina. Patients in both groups were of a similar age and had had Crohn's disease for a similar period before diagnosis of perianal involvement. The incidence of associated perianal lesions, superficial ulcers, cavitating ulcers, other fistulas and strictures was not significantly different between the two groups. A greater proportion of patients with anorectal–vaginal fistulation* (n = *15*) *had distal intestinal Crohn's disease* (*rectal or contiguous colorectal*) *compared with women with no vaginal fistulation* (n = *14*). *A range of therapies was used to manage women with perianal Crohn's disease, from local surgery to a defunctioning stoma and/or proctectomy. Only 13 of 38 women with perianal Crohn's disease but no vaginal fistula required a defunctioning stoma or proctectomy, whereas 18 of 29 with anorectal–vaginal fistulation underwent these procedures* ($P < 0.05$). *A vaginal fistula has a considerable adverse effect on the outcome of perianal Crohn's disease.*

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Anovaginal and rectovaginal fistulation occurs in 9 per cent of women with Crohn's disease[1]. This complication is the source of distressing morbidity and embarrassing vaginal faecal discharge in women who are often young. Many techniques for managing the symptoms of anorectal–vaginal fistula in this situation have been described[1–5].

A standardized method of classifying perianal Crohn's disease[6] was used to define two groups of women, one with anorectal–vaginal fistula and the other without vaginal involvement. Patients in each group had details of perianal and proximal intestinal disease recorded prospectively in a standard fashion with details of therapy. The aim was to compare the pattern of perianal Crohn's lesions and intestinal Crohn's involvement, the management of perianal disease, and the outcome for women with and without Crohn's anorectal–vaginal fistulation.

Patients and methods

Between 1971 and 1991, 135 patients had details of perianal Crohn's disease recorded prospectively; 67 were women The description of perianal involvement was codified according to the Cardiff classification of perianal Crohn's disease[6,7] Details of proximal intestinal Crohn's disease identified by radiology, endoscopy or surgery were noted The surgical procedures used and clinical outcome were obtained for each patient

Comparisons between the two groups of patients with perianal Crohn's disease with and without anorectal–vaginal fistulation were made using the χ^2 test

Results

A group of 67 women were identified with perianal Crohn's disease. Anovaginal (Cardiff classification F3A) or rectovaginal (Cardiff classification F3B) fistulation was present in 29 women (43 per cent). A total of 38 women (57 per cent) had perianal Crohn's disease but without a vaginal fistula. The median age (36 *versus* 36 5 years) and duration of disease at diagnosis (3 *versus* 2 years) were similar for patients with and without vaginal fistulation The median follow-up for women with and without vaginal fistulation was similar (4 *versus* 5 years). The proportion of patients in each group considering themselves free of symptoms after this time was also similar.

Patterns of perianal Crohn's disease were compared for women with and without anorectal–vaginal fistula. The groups had a similar incidence of anorectal superficial ulceration, cavitating ulcers, other perianal fistulation and anal stricture (*Figure 1*).

Women with anorectal–vaginal fistulation had a higher incidence of distal intestinal (rectal or contiguous colorectal) Crohn's disease ($n = 15$) than those without vaginal fistula ($n = 14$) (*Figure 2*) This difference was not statistically significant

A wide range of therapies was employed (*Figure 3*). Management was determined by clinical assessment. Overt sepsis was treated by antibiotics and conservative drainage. Low fistulas were laid open and high fistulas usually treated using a seton Anterior high fistulas in patients with inactive

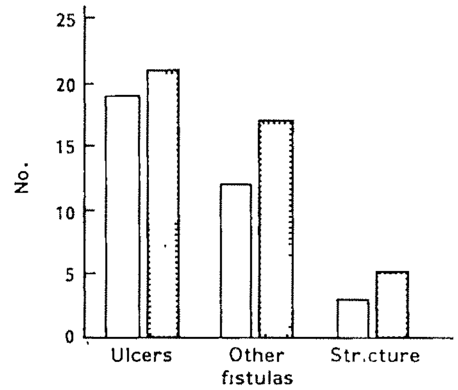

Figure 1 *Comparison of perianal Crohn's disease lesions in women with* (□) *and without* (⬚) *anorectal–vaginal fistulation Ulcers, superficial or cavitating, other fistulas, perianal fistulas not involving the vagina, stricture, anal, rectal or extrarectal narrowing* (*all following Cardiff classification*[7])

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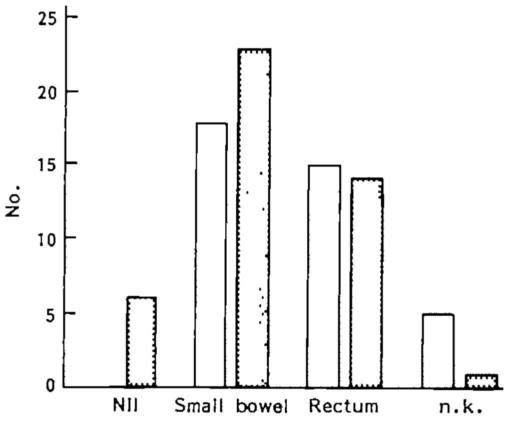

Figure 2 *Distribution of intestinal Crohn's disease in women with (□) and without (▨) anorectal–vaginal fistulation. Nil, no intestinal disease, small bowel, small intestinal and/or proximal colonic disease, rectum, rectal and/or contiguous distal colonic disease, Crohn's disease of the rectum involving the left colon in continuity, n.k, insufficient assessment*

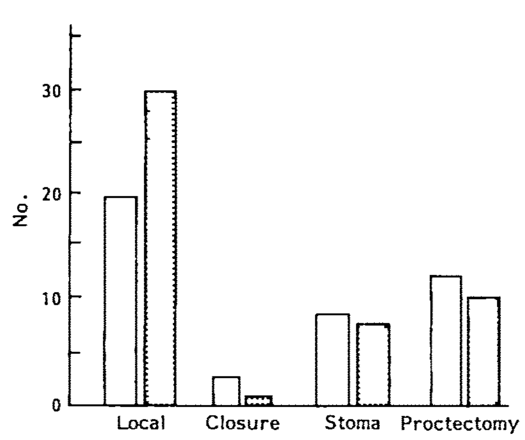

Figure 3 *Use of different therapies in women with (□) and without (▨) anorectal–vaginal Crohn's fistulation Several patients received more than one therapy Local surgery included dilatation, steroid injection, laying open of fistula and drainage of abscess Closure, closure of internal opening, stoma, proximal diverting stoma formation*

Crohn's disease have been treated recently by a musculomucosal advancement flap[8]. Patients with severe pain, in the absence of sepsis, that was unresponsive to antibiotics were treated by Depo-Medrone (methylprednisolone) injection (Upjohn, Crawley, UK)[9]. Rectal excision was used for uncontrollable symptoms in the presence of active Crohn's disease and after failure of a defunctioning stoma to control disease activity.

Patients with anovaginal or rectovaginal fistulation had more surgery than those with perianal Crohn's disease without vaginal involvement. Two-thirds of the latter were managed satisfactorily with medical therapy or local surgery alone, compared with only 12 of those with vaginal fistulation (*Figure 3*).

Defunctioning stomas were employed more commonly in women with anorectal–vaginal fistula than in those without vaginal fistulation, and a higher proportion required proctectomy. The need for a defunctioning stoma or proctectomy was more common in patients with vaginal fistula than in those without ($\chi^2 = 5{\cdot}14$, 1 d.f., $P < 0{\cdot}05$). In the majority of women with vaginal fistulation undergoing proctectomy (seven of 12), the severity of the symptoms from the anorectal–vaginal fistula was the main indication for rectal excision.

A separate comparison was made between women with anovaginal ($n = 14$) and rectovaginal ($n = 15$) fistulation. Patients in both groups were of similar age and duration of disease at presentation and had a similar length of follow-up. Patients with rectovaginal fistula had a higher incidence of cavitating Crohn's ulceration and stricture than those with anovaginal fistula, although this difference was not statistically significant. The use of rectal excision was more frequent in patients with rectovaginal fistulation (eight of 15) than in those with anovaginal fistula alone (four of 14).

Discussion

Anal and rectal fistulation into the vagina in women with Crohn's disease is not uncommon. Several descriptions of the varied clinical course of vaginal fistulation in those with perianal Crohn's disease exist[1–5], but these have not classified perianal Crohn's disease in a standardized prospective fashion. It has therefore not been possible to determine whether Crohn's anorectal–vaginal fistulation is associated with a different severity of perianal disease, a different pattern of intestinal Crohn's disease or a different therapeutic outcome. The present study shows that anorectal–vaginal fistulation is not associated with a different pattern or severity of perianal Crohn's disease, and that distal intestinal Crohn's disease is not significantly more common in women with vaginal fistula.

The frequency of proctectomy in this study for patients with vaginal fistulation is the same as that described before (42–51 per cent)[1–3] and confirms the view that anorectal–vaginal fistulation does not mandate removal of the rectum[4] Vaginal fistula is, however, associated with a significantly higher risk of a defunctioning stoma or proctectomy.

Symptoms from the vaginal fistula were the main indication for surgery in most of the patients treated by rectal excision. Rectovaginal fistula produced more symptoms of faecal loss than did anovaginal fistula. When symptoms from vaginal fistulas are the most important factor in determining surgery, newer techniques of anorectal–vaginal fistula closure[5], in patients with locally quiescent disease, may reduce the use of proctectomy.

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Manual dilatation of the anus

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A group of 100 consecutive patients undergoing manual dilatation of the anus between 1980 and 1983 were reviewed retrospectively by examining the clinical presentation, diagnosis, treatment and outcome. Anal fissure was diagnosed in 46 patients, 22 had either first- or second-degree haemorrhoids, and stenosis of the anal canal was identified in seven. Manual dilatation of the anus was performed on 25 patients in the absence of a diagnosis. Dilatation failed to treat 26 anal fissures successfully. Where it was employed alone in ten cases of haemorrhoids and seven of anal stenosis, manual dilatation failed to cure seven and five patients respectively. Of the patients with no diagnosis, 23 were relieved of their symptoms following dilatation. Episodes of incontinence occurred in 27 patients, 21 of whom were female. There should be a reduced role for manual anal dilatation in the treatment of common anorectal disorders.

Manual dilatation of the anus was first described by Recamier in 1829 for the management of anal fissure[1]. Its reintroduction by Goligher to treat this condition[2] and its popularization by Lord for third-degree haemorrhoids[3] has led to this procedure becoming an accepted first-line therapy. The gentle controlled manual dilatation of Goligher and colleagues[2] and the more aggressive approach of Lord[3–5] have been supported by some[6], but the rationale, efficacy and complication rate have been questioned by others[7,8].

The presentations, indications for, results and complications of manual anal dilatation used in the management of 100 consecutive patients presenting with anal canal symptoms during a 3-year period were therefore reviewed.

Patients and methods

The case records of 100 consecutive patients who underwent examination under anaesthesia and manual dilatation between 1980 and 1983 were reviewed retrospectively The clinical presentation, diagnosis at examination under anaesthesia and treatment were recorded.

During the follow-up period three patients died from unrelated causes The remaining 97 patients were sent questionnaires asking about the incidence of uncontrolled passage of flatus and/or mucus leak or slight soiling of underwear (minor incontinence) or uncontrolled passage of faeces (major incontinence). Efficacy was assessed by reviewing the case notes to see how many times manual dilatation was repeated during the follow-up period Postoperative morbidity was assessed from the questionnaire and related to the patient's status at the time of follow-up.

Table 1 *Previous surgery in patients undergoing manual dilatation of the anus*

Procedure	No
Haemorrhoidectomy alone	12
Haemorrhoidectomy and manual dilatation	1
Manual dilatation alone	12
Manual dilatation and excision of fissure	1

Results

The mean age of the patients studied was 36 (range 4–79) years; 52 were male. Before the study period, 16 patients had undergone surgery, 12 of whom had had manual anal dilatation as a separate procedure (range 1–9 times) (*Table 1*). Of the patients, 79 presented with proctalgia and rectal bleeding, 13 with proctalgia alone, seven with rectal bleeding alone and one with constipation.

The diagnoses at examination under anaesthesia are shown in *Table 2*; 46 patients had an anal fissure, 22 had first- or second-degree haemorrhoids, and stenosis of the anal canal was found in seven. Manual dilatation was performed on 25 patients who had no abnormality identified at examination under anaesthesia.

The median follow-up was 90 (range 76–100) months. Three patients died, nine had left the area and of the 88 possible replies, 55 were received, giving a response rate of 62 per cent.

Manual anal dilatation failed to relieve symptoms in 26 of the 46 patients with anal fissure: 23 underwent repeat dilatation within 1 year, two within 2 years and one at 5 years. These 46 patients underwent a total of 116 manual dilatations (range 1–10 each) during the follow-up period.

Where dilatation had been used with phenol injection in the management of 12 patients with haemorrhoids, two required further treatment (one repeat injection, one banding). Of the remaining ten patients who had manual anal dilatation alone, seven required further treatment (five haemorrhoidectomy, two banding). Dilatation was unsuccessful in treating five of seven patients with anal canal stenosis despite the procedure being repeated three to eight times during the follow-up period. Twenty-three of the 25 patients in whom no abnormality was detected at examination under anaesthesia were asymptomatic

Table 2 *Preoperative diagnosis, management and outcome in patients undergoing manual dilatation of the anus*

			Outcome		
Diagnosis	No	Management by dilatation alone	Repeat dilatation	Major incontinence	Minor incontinence
Anal fissure	46	46	26	2	9
Haemorrhoids	22	10	7	0	2
Anal stenosis	7	7	5	4	3
Normal examination under anaesthesia	25	25	0	1	6

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Table 3 *Incidence of incontinence in male and female patients following manual dilatation of the anus*

Incontinence	No	Male ($n = 22$)	Female ($n = 33$)
Major	7	1	6
Minor	20	5	15

after manual anal dilatation. Two patients were discharged with persisting proctalgia

Twenty-seven of the 55 patients who returned a questionnaire complained of incontinence (minor in 20, major in seven) (*Table 2*). Six of the seven cases of major incontinence resulted from two or more dilatation procedures. Of the 25 patients in whom no pathology was detected, six developed minor and one major incontinence. Manual anal dilatation was complicated by anal stenosis in one patient. Both minor and major incontinence occurred more frequently in women following dilatation (*Table 3*)

Discussion

Manual dilatation of the anus is a widely accepted treatment option for anal fissure and haemorrhoids. The efficacy and complication rate of Lord's procedure have been variously contested when it is compared with other treatment options[9–12]. In this study the use of such dilatation for the treatment of anal fissure resulted in a recurrence rate of 57 per cent. A similar number were not helped by a second anal stretch. This recurrence rate exceeds that of previous studies[2,9,10], but may be explained by the higher proportion of chronic fissures and the longer follow-up period covered

The high failure rate for manual dilatation alone in the management of haemorrhoids could be accounted for by poor case selection in light of the observation that five of the seven patients subsequently required formal haemorrhoidectomy This is in contrast to the two patients whose symptoms returned after treatment with injection and dilatation, one requiring repeat injection and the other being successfully treated with banding. In view of the small numbers in this group, no comment can be made on efficacy.

Stenosis of the anal canal is a difficult clinical problem to deal with, but this review clearly indicates that long-term improvement is not maintained following repeated manual dilatation.

In this study, manual anal dilatation was carried out on 25 patients without indication, giving credence to the authors' belief that the examination under anaesthesia has become synonymous with the anal stretch in general surgical practice. It may be that these patients had acute pathology that resolved before admission.

When compared with other treatments, dilatation for the management of haemorrhoids and fissures has had its proponents and critics. Walls and Ruckley[13] reported a 75 per cent 'success' rate for the procedure at 5 years Their results are supported by Sandilands *et al.*[14], who reported that pain and bleeding were more successfully treated than prolapse Keighley *et al.*[15] and Arabi *et al.*[16] indicated that the best results might be obtained in patients with high pressure in the internal sphincter, while others have counselled caution in using the procedure in the presence of low anal tone or rectal prolapse[8,17].

The present finding of most concern was that 27 patients developed a degree of incontinence after manual dilatation. This exceeds the incontinence rate of some reported series[2,3,10–12] but is comparable to that of others[18] The reason for the poor results of the present review may lie in the longer follow-up period than other studies[2–4] or may be due to patients being asked more appropriate questions regarding 'soiling of underwear' or 'uncontrolled passage of mucus/wind from the back passage' as opposed to 'episodes of faecal incontinence'[3,4].

A recent study using endoanal ultrasonography may explain incontinence after manual dilatation by demonstrating disruption of the internal anal sphincter[19]. Women are particularly vulnerable because childbirth results in pelvic floor weakness with perineal descent and external sphincter neuropathy[20].

The variable results and long-term sequelae of dilatation may be operator dependent as not all surgeons religiously follow the procedure as originally described[2,3]. In this series, dilatation was performed in different ways by different surgeons and the poor results may reflect this. A more forceful dilatation, though treating more fissures and haemorrhoids, may have resulted in an even greater incontinence rate

In conclusion, manual anal dilatation failed to treat successfully the majority of common anorectal disorders. Without a clear pathophysiological understanding of anal fissure and on the assumption that haemorrhoids are prolapsing anal canal cushions, the rationale for stretching the internal sphincter is unclear[21] There are alternative treatment options for fissure and haemorrhoids and, because incontinence is such a distressing complication, manual dilatation of the anus should not be carried out, especially in female patients.

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Limitations of laser treatment for malignant dysphagia

Sir

We read with interest the recent paper by Dr Shmueli and colleagues on the limitations of laser treatment for palliation of malignant dysphagia (*Br J Surg* 1992; **79**: 778–80). Our own results are similar. Between January 1989 and August 1992, 67 patients (45 men, 22 women) of mean age 71 (range 41–91) years underwent palliative endoscopic laser ablation of obstructing oesophageal carcinoma. The mean survival from diagnosis was 6 (range 1–25) months.

Our experience differs from that of Shmueli *et al.* in two important aspects. First, the vast majority of laser treatments were performed on an outpatient basis. Second, we prevented recurrent dysphagia by early follow-up endoscopy with laser ablation where necessary. Patients underwent a mean of 3 sessions, with an interval of 5 (range 1–18) weeks between them.

Our complication rate was slightly less at 6 per cent; three patients sustained oesophageal perforation following dilatation before laser therapy. All were recognized and treated successfully with open insertion of a Celestin tube and antibiotic prophylaxis. At the second therapy session, one patient developed severe haemorrhage, which it was not considered appropriate to treat. Patients with tumours well above the gastro-oesophageal junction were technically easier to treat and remained symptom-free, eating a normal diet between treatments.

In conclusion, we agree that endoscopic laser therapy provides excellent palliation of obstructive carcinoma with an acceptable complication rate and does not preclude later intubation if required.

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Functional evaluation of the intrathoracic stomach as an oesophageal substitute

Sir

The recent article by Dr Bonavina and co-workers (*Br J Surg* 1992; **79**: 529–32) addressed the important question of how to evaluate function of the intrathoracic stomach in patients following oesophagectomy. The results obtained from the radionuclide transit studies, however, and similar data reported from a larger series of patients from our institution[1], do not support the conclusion that the interposed stomach 'acts like an inert tube'.

Radionuclide scintigraphy has seen increasing application in the physiological assessment of the upper gastrointestinal tract, and may be more advantageous for evaluating function of the neo-oesophagus than conventional imaging techniques. The significantly lower gastric half-emptying time ($t_{1/2}$) reported for the 12 patients studied in comparison with six healthy controls (mean $t_{1/2}$ 26 *versus* 45 min) may be an artefact related to the difference between a vertical intrathoracic stomach and the relatively horizontal abdominal stomach in controls. In our studies[1], no significant difference in gastric emptying was observed between patients with an intrathoracic stomach and healthy controls (mean $t_{1/2}$ 43 *versus* 45 min). Although direct comparison between patient groups may not be possible because of differences in the technical aspects of oesophageal resection (transhiatal *versus* transthoracic), reconstruction (hand-sewn cervical anastomosis *versus* stapled intrathoracic), patient numbers and standard meal used, comparable rates of gastric emptying for control patients were found in both studies, and failure to consider such potential attenuation artefacts, technical or anatomical factors may well account for the apparently rapid gastric emptying reported. However, even with such reported emptying rates (mean $t_{1/2}$ 26 min), we conclude that the vagotomized intrathoracic stomach appears to retain its gastric identity rather than functioning as an inert conduit.

Our studies also showed that patterns of gastric emptying were complex, with marked variation in the anatomy of the intrathoracic stomach, motion of the labelled solid or liquid bolus and rates of spontaneous emptying. Little correlation was found between postoperative symptoms and objective findings. All patients were able to swallow satisfactorily, further supporting the use of stomach as an oesophageal substitute following oesophagectomy.

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Authors' reply

Sir

I read with interest the comments of Dr Casson and colleagues. Unfortunately, their paper had escaped our attention at the time we were working on the manuscript. In support of our opinion that the transposed stomach acts like an inert tube, I would like to reply as follows.

The gastric emptying rates reported in our study compare well with data of other investigators who used a radioactive semisolid meal[1]. It has previously been shown that rapid initial gastric emptying occurs in the intrathoracic stomach, and this phenomenon may represent a delay in receptive gastric relaxation due to vagotomy[2]. Interestingly, in a randomized trial comparing pyloroplasty *versus* no drainage[3], the emptying time of a semisolid meal was lower in patients with pyloroplasty, suggesting that decreased outflow resistance may promote gastric emptying. That gravity further accelerates emptying of the intrathoracic stomach is clearly demonstrated by another study showing slower emptying in the supine than the upright position of a dual-labelled isotopic meal[4].

In the patients in our original series, no propagated motor activity was recorded manometrically within the intrathoracic stomach. This finding is in agreement with the results of others[5] and indicates that the transposed stomach does not actively contribute to bolus progression.

From these observations it is difficult to support the contention that the intrathoracic stomach retains its physiological identity, especially when a gastric drainage procedure is added. However, I share the opinion of Dr Casson and colleagues that the stomach remains the best oesophageal substitute following oesophagectomy for cancer. Despite the potential for postoperative functional abnormalities, symptoms and/or mucosal lesions in about one-third of patients, most individuals resume a near-normal diet after oesophagogastrostomy and quality of life is satisfactory.

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Mesosigmoplasty as a definitive operation for sigmoid volvulus

Sir

We read with interest Dr Subrahmanyam's article on mesosigmoplasty as a definitive operation for sigmoid volvulus (*Br J Surg* 1992; **79**: 683–4). He is to be congratulated on the remarkably low mortality and recurrence rates achieved when treating the emergency sigmoid volvulus by the method described. We have recently studied 30 patients with sigmoid volvulus who presented as emergencies to Nottingham hospitals over the past 4 years. The mean age was 70 (range 40–96) years; the sex distribution was equal. In all cases, the diagnosis was made from clinical features and abdominal radiography. Flatus tube decompression was attempted in all patients and was considered to produce an acceptable result in 15. A total of 15 patients underwent operation for an emergency sigmoid volvulus during the presenting admission; the sigmoid colon was always resected, whether gangrenous or not. In seven patients a defunctioning colostomy and mucus fistula was formed and in eight a primary anastomosis was fashioned, none with covering colostomies. In this last group there were two anastomotic leaks and one small bowel obstruction. Overall, nine patients died: five from the group treated conservatively, one among those who had a defunctioning colostomy and three from the group undergoing primary anastomosis. To date there have been three recurrences, all occurring in patients initially treated conservatively. They have been managed with surgical resection of the sigmoid colon and primary anastomosis.

Our audit reveals morbidity, mortality and recurrence rates higher than those of Dr Subrahmanyam, although this can be explained by the cohort being older and in poor general health. The mesosigmoplasty operation is a valued addition to the treatment options available to manage sigmoid volvulus.

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Perforation of the bowel by suction drains

Sir

We read with interest the Case Report by Mr Reed and colleagues (*Br J Surg* 1992; **79**: 679) on injury to the bowel caused by suction drains. We have recently had two similar cases.

In the first, a 63-year-old man was admitted with peritonitis. He had previously undergone total cystectomy and ileal conduit. At operation a perforated sigmoid diverticulum was found. Hartmann's procedure was performed and a 2·5-mm suction drain inserted into the pelvis. After 5 days, a biliary leak through the wound and drain developed. At laparotomy the patient had two focal perforations in the small bowel and two other areas of focal necrosis of the serosa and muscle. These lesions were lying against corresponding holes in the suction drain. The bowel was repaired and the patient has since been discharged.

In the second case, an 80-year-old man was admitted for Hartmann's procedure for carcinoma of the rectum. The pelvis was packed with ribbon gauze to control generalized oozing, and a larger suction drain (5 mm) was left in the gauze. The gauze was removed 2 days later. The following day peritonitis and a biliary leak through the wound developed. At laparotomy there were two perforations in the small bowel similar to those already described (*Figure 1*). There was also a transverse tear in the small bowel that was thought to have been caused by removal of the ribbon gauze with the suction drain still in place. The patient had a stormy postoperative recovery and died nearly 2 months later.

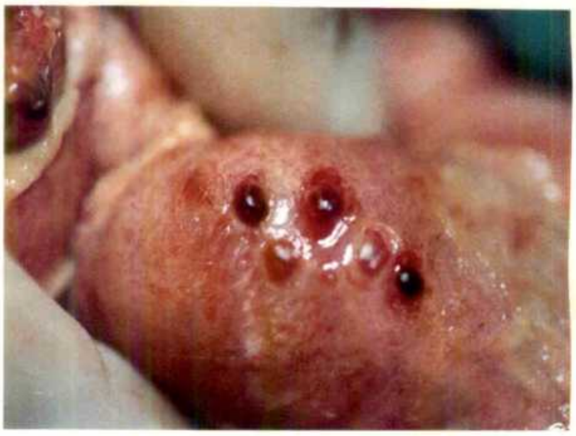

Figure 1 *Suction injuries of the small bowel*

These injuries have occurred since we replaced glass bottles with flexible rubber tops by rigid plastic bottles that do not 'give' at all. We have since reverted to sump, tube and corrugated drains for laparotomy for bowel surgery. Suction drains are not without their hazards, and we have now issued appropriate warnings to the supply department.

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Screening for large bowel neoplasms in individuals with a family history of colorectal cancer

Sir

Mr Dunlop (*Br J Surg* 1992; **79**: 488–94) deduces from a review of seven papers (not in fact all those that explore the subject) that flexible sigmoidoscopic screening is inappropriate for those at risk of colorectal cancer because of a family history of the disease. We would like to comment on this conclusion.

First, there are a number of misinterpretations of the literature. He points out that McConnell *et al.*[1] would have missed six lesions (size not given) by screening with the flexible sigmoidoscope; however, this figure represents only 4·8 per cent of the individuals screened. These data imply that 95 per cent of the patients screened may have undergone unnecessary colonoscopy with its inherent risks. More importantly, he fails to include in his analysis McConnell's report[2] of a further 130 individuals in whom only two lesions (size again not given) were found proximal to 55 cm. Mr Dunlop states that Grossman and Milos[3] would have missed lesions in 16 of 28 individuals. However, in their paper they state that 43 per cent of lesions were beyond the reach of the flexible sigmoidoscope, which may not mean that lesions were missed in 43 per cent of individuals. Furthermore, he seems to have failed to note that this study excluded all individuals with rectal disease. In addition, only 4·5 per cent of lesions found were $\geqslant 5$ mm in size, so, until the significance of diminutive polyps is understood, it is unwise to draw too many conclusions from this finding. 'Inferred data' were calculated from an abstract[4] to guess how many lesions would have been found in the randomization process involved and, as such important details as age and strength of family history of those who did and did not proceed to colonoscopy are not stated, this inference is open to question.

Second, although Mr Dunlop points out that it is possible to stratify the risk to which a particular individual is exposed, he fails to mention that it is therefore eminently possible to tailor screening protocols to suit individual needs

Third, it is stated that individuals with a family history of colorectal cancer have a propensity to develop right-sided lesions Although this is the case for hereditary non-polyposis colorectal cancer, there is no evidence that it is so for those with a familial tendency.

Finally, he points out that it is inappropriate to carry out an incomplete examination on screened patients and thereby perhaps give false reassurance. We would agree with this general sentiment but must point out that he has partly based his viewpoint on a study that found no more pathology in these people than in the general population[3]. Colonoscopy is an investigation with a morbidity and mortality rate We believe that the evidence to advocate a 'blanket' policy of colonoscopy for all levels of family risk has not been shown by the currently available data

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4 Herrera L, Hanna S, Petrelli N, Nava H Screening endoscopy in patients with a family history positive (FH^+) for colorectal neoplasia (CRN). *Gastrointest Endosc* 1990; **36**: 211 (Abstract)

Author's reply

Sir

Miss Hunt and Mr Armitage fail to note that the paper by McConnell *et al.*[1] reported data on 125 individuals who were negative on faecal occult blood (FOB) testing and had no prior history of colorectal neoplasms A total of 106 individuals were excluded who had a positive family history but were FOB-positive and/or who had a prior history of neoplasms, because they stated that colonoscopy would be required in these anyway The comment that 95 per cent of this group underwent unnecessary colonoscopy is countered by the fact that this was a highly selected cohort

The suggestion that inference from the data of Herrera *et al*[2] was guesswork seems somewhat harsh. Nineteen of the original 200 patients with a positive family history were found to have polyps on flexible sigmoidoscopy. All 181 patients negative on flexible sigmoidoscopy were invited for colonoscopy and 70 accepted Seven (10 per cent) had neoplasia, one with cancer Even if none of the remaining 111 patients who declined colonoscopy had proximal neoplasia, the sensitivity of flexible sigmoidoscopy in the total study group was 73 per cent but missed the only cancer in the study group. However, I stand by the inferred data since there is no reason to suspect a systematic bias in individuals accepting colonoscopy The inferred prevalence of neoplasia detectable only by colonoscopy in the 181 patients who were negative on flexible sigmoidoscopy was 21 per cent This is simply an extrapolation from the 70 actually examined.

Since any screening of first-degree relatives of affected individuals will be, by definition, prospective, it will not be known which of the families are actually hereditary non-polyposis colorectal cancer families, and so the comments on right-sided propensity are to some extent irrelevant.

I agree with Hunt and Armitage that many of the published studies either do not mention polyp size or include smaller polyps in the analysis. We do not know the importance of such lesions when a family history of colorectal cancer is present However, the combination of results from studies cited in this review includes small and large polyps detected by flexible sigmoidoscopy or colonoscopy, and so the comparison of detection rate is valid Clearly there is morbidity and mortality associated with any invasive procedure such as colonoscopy, but this must be balanced against the need to do anything at all. It should be noted that, when a patient who has a positive family history of colorectal cancer is being screened by sigmoidoscopy alone, the data suggest that if they do actually have a tumour in the colon or rectum there is only a 50–60 per cent chance of detecting it

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Mechanism of action of external compression on venous function

Sir

We read with interest the paper by Sarin and colleagues (*Br J Surg* 1992, **79**. 499–502) that examined venous reflux in 57 limbs while a pressure cuff was inflated around the knee The authors demonstrated that in 15 limbs venous competence was restored before complete venous occlusion, concluding that compression therapy acts by restoring competence to dilated incompetent valves. However, a pressure of 40 mmHg at the knee restored venous competence to only five of the 57 limbs (9 per cent) Since most compression stockings exert this pressure or less at the ankle, reducing towards the knee, this surely suggests that such stockings do not act by restoring valvular competence.

We have studied venous reflux in 22 incompetent major calf veins of 19 limbs by duplex ultrasonography with and without grade 2 compression stockings We found that the compression stockings reduced peak reflux velocity and venous diameter, but restored competence in only two veins (9 per cent). one restored to complete competence and in one the duration of reflux was reduced to <0·5 s In our opinion these studies both suggest that compression hosiery does not act by restoring competence to dilated incompetent venous valves.

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Authors' reply

Sir

Mr Payne and colleagues are entirely correct in expressing concern that compression hosiery may not act by restoring competence to valves in large veins We are grateful to them for presenting data that cover an issue not addressed in our original paper, i.e. the effect of applying compression hosiery to the competence of large-sized veins. In our study we deliberately avoided compressing the limb distal to the level of the hydraulic cuff so as to separate the local effect of compression from that of total limb compression, making direct comparison between our cuff and hosiery difficult We demonstrated that at an external compression pressure of 40 mmHg, only 9 per cent of veins were restored to competence and that at a higher pressure up to 27 per cent regained competence Although the pressure exerted by hosiery at the ankle at rest is <40 mmHg, the pressures achieved while the patient is walking are higher, particularly at the crucial stage of 'calf systole'.

This mechanism may result in more veins regaining competence, thereby improving venous function. Neither of our studies addressed the question of whether small-sized veins (1–2 mm in diameter) are restored to competence by external compression, a mechanism that we suggested may explain the plethysmographic findings of some authors who have shown improved venous function following application of compression hosiery Finally, Mr Payne and colleagues also mention that the application of compression hosiery reduced the peak reflux velocity. This may be due simply to the fact that stockings raise the interstitial tissue pressure, resulting in a reduced pressure gradient in the veins along the limb, or alternatively that external compression does indeed restore competence in small-sized veins Our own feelings are that, while compression hosiery may act by restoring competence in large veins, it is unlikely to explain the overall efficacy of compression therapy, and we have turned our attention to investigating the effect on the microcirculation of the skin This part of the circulation seems to be much more directly influenced by local compression than do the large veins

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Pylorus-preserving *versus* standard pancreaticoduodenectomy: an analysis of 110 pancreatic and periampullary carcinomas

Sir

We note with interest the article by Dr Roder and colleagues (*Br J Surg* 1992, 79 152–5) comparing pylorus-preserving pancreaticoduodenectomy (PPPD) with standard pancreaticoduodenectomy (PD) in the treatment of 110 pancreatic and periampullary carcinomas This report is an important effort in the evaluation of the new pylorus-preserving operation, which has joined a wide range of optional procedures in the treatment of these malignancies

The authors found that there was no difference in the survival rate of patients undergoing PPPD or PD with partial gastrectomy for stage I pancreatic and periampullary cancers. This finding is in spite of the fact that there was a bias in favour of the standard PD operation, since 24 of 62 patients (39 per cent) had a favourable tumour grade for PD and only nine of 48 (19 per cent) for PPPD This difference is significant at $P = 0\ 02$ (Miettinen's modification of Fisher's exact test)

For patients with stage III tumours, there did not appear to be any tendency for bias as to tumour grade or staging for either pancreatic or periampullary carcinoma This report suggested that there was a significantly improved survival with PD *versus* PPPD for stage III carcinoma of the pancreas but not for periampullary cancer This difference was apparent for up to 26 months, the survival rate for PD was <10 per cent at 5 years

According to the classification used by Roder and colleagues, stage III tumours had one or more positive nodes and included patients in whom the tumour extended directly to either the stomach, spleen, colon or adjacent large vessels (T_3) It is our practice not to resect carcinomas of the pancreas if they are classified T_3 either before operation or at exploration We would, therefore, agree that the pylorus-preserving procedure should not be applied as a palliative resection or cure in patients with a T_3 tumour The authors have not given a breakdown of stage III cases as to T status. Their resectability rates of 30 per cent overall, 48 per cent of cases fit for surgery and 83 per cent of those thought suitable for resection before operation are quite high and indicate that a significant proportion of resected tumours are T_3. Indeed, whether any resection is advisable for T_3 pancreatic lesions is open to question

In another vein, the follow-up in these patients was a median of only 24 (range 8–92) months The Kaplan–Meier statistical technique was used It would be interesting to see what the actual survival rate was after all cases had been followed up for 5 years or more

The only way these questions can be answered is with a strictly prospective blind study in which rigid protocols are followed in the decision-making process as to the operation performed, and the decision is not left to the individual surgeon's preference (five in this report) Ideally, in addition follow-up should extend for 5 years in all cases

In summary, we applaud the effort of the authors in attempting to shed light on the controversy as to what the extent of resection should be in the attempted cure or palliation of cancers of the pancreas, a question that we feel is as yet unanswered

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Authors' reply

Sir

We appreciate the comments of Drs Braasch and Rossi and thank you for the opportunity to reply

As outlined in the paper and according to international agreement, periampullary tumours (i e. those of the papilla of Vater and the distal portion of the common bile duct) and adenocarcinoma of the head of the pancreas are two different entities with significant differences in prognosis When analysing the effect of various operative procedures, these tumours should therefore be evaluated separately. The significant difference in the distribution of tumour grade between patients who had a standard or pylorus-preserving pancreaticoduodenectomy (PPPD), which was noted by Drs Braasch and Rossi, exists only when periampullary tumours and those of the pancreatic head are evaluated as one group When these tumours are evaluated separately, as in our study, there is no significant difference in grading between the two types of operation

The presence of a T_3 tumour can frequently be diagnosed only during operation once the procedure has progressed beyond the 'point of no return' This is particularly so with infiltration of the portal or superior mesenteric veins Nine of the 53 patients with carcinoma of the pancreatic head had a T_3 tumour In seven of nine patients the tumour infiltrated the portal vein, in two there was infiltration of the superior mesenteric vein Of the nine patients, five had a standard pancreaticoduodenectomy (PD) and four underwent PPPD Consequently, there was no difference in the distribution of T_3 tumours between the procedures

Finally, we agree with Drs Braasch and Rossi that the controversy between pylorus-preserving and standard PD in patients with malignant disease can ultimately be decided only by a prospective randomized study Based on our observations, standard PD with distal gastric resection remains, however, the procedure of choice for resection of carcinoma of the head of the pancreas at this institution, for the time being

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Technique for laparoscopic appendicectomy

Sir

We read with interest the recent Surgical Workshop by Mr Byrne and colleagues on laparoscopic appendicectomy (*Br J Surg* 1992, 79· 574–5) We applaud the lack of complications in the 25 patients but are concerned about the potential risk of infection The method was originally described by Browne[1] in 1990, who reported a wound infection rate (superficial wound abscess requiring drainage) of 7 per cent in 100 patients This accords with our own early experience of one wound infection in seven cases, which led us to discontinue the technique We now prefer to deliver the appendix into a waterproof bag before removal from the abdomen or via the right-hand 11-mm cannula (if the appendix is small enough), avoiding contact with any wounds

Another worry is that, when attempting to deliver a friable appendix, fragmentation could occur resulting in peritoneal contamination In obese patients or those in whom the mesentery is short, difficulty may also be encountered when attempting this procedure

The mean operating time of 62 min does not show any advantage over the intra-abdominal method of laparoscopic appendicectomy, although we accept that this time would probably decrease with experience Unless further large studies show the safety and efficacy of this technique, we feel it cannot be recommended as the method of choice for removing the appendix laparoscopically.

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1. Browne DS. Laparoscopic-guided appendicectomy. A study of 100 consecutive cases *Aust N Z J Obstet Gynaecol* 1990; **30**: 231–3.

Authors' reply

Sir
We thank Messrs Loh, Loosemore and Taylor for their comments As described in our paper, we too aim to avoid contact between the inflamed appendix and wound edges by withdrawing the appendix into the right iliac fossa cannula before delivering it on to the skin We believe that this can reduce the incidence of wound sepsis encountered by Browne[1], who delivered the appendix directly through the wound after an incision in the right iliac fossa, a technique different from the one we described.

In the series reported, we were able to deliver friable appendices to the surface by grasping them closer to the caecum Mobilization of the caecum also facilitates this process where the mesoappendix is short. We recognize, however, that these circumstances together with obesity of the patient can present serious difficulties. Consequently, we do not advocate this as the method of choice for all appendicectomies but rather as an option, especially suited to cases of early inflammation of a mobile appendix.

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1 Browne DS Laparoscopic-guided appendicectomy. A study of 100 consecutive cases. *Aust N Z J Obstet Gynaecol* 1990, **30**: 231–3

Book reviews

A Manual for Acute Postoperative Pain Management

F. B. Sevarino and L. M. Preble 240 × 160 mm Pp. 242. Illustrated. 1992 New York: Raven Press. US $69.

The surgical patient usually complains of pain after operation; this is not always treated by the best methods currently available. The old approach of administering intramuscular opiate drugs, often when convenient to the nursing staff, has now been replaced by other techniques, including patient-controlled analgesia, epidural infusion of local anaesthetics or opiates, and non-steroidal anti-inflammatory drugs. Many hospitals in the UK are now recognizing that introduction of an acute pain service using these techniques cannot be achieved without proper training and teaching of nursing and medical staff.

This book describes the approaches used by the hospitals of the Yale University School of Medicine. It is written by a clinician (the Associate Director of the Acute Pain Service) and a nurse (who acts as the Clinical Administrator of the Service). They clearly draw on a wealth of experience and have produced a book of two distinct parts. The first is a didactic approach – 'how we do it' – with a number of appendices addressing the issues of nursing and physician education, patient education, administration records and flowsheets. In the second part, the individual techniques available are further discussed, together with a final chapter of illustrative cases in which acute pain management has presented specific problems.

Although the science and the message are lucidly discussed, I have doubts over whether British clinicians will really find favour with this very American-style didactic textbook. This does not mean that they should not read it, but some of the problems highlighted in the USA will need to be addressed in a different way in the UK. It is to be hoped that the 'marketing of an acute pain service' will not be an issue in the UK that governs the efficacy with which we provide pain relief to our patients.

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Lung and Heart–Lung Transplantation

V. Gallucci, U. Livi, G. Faggian and A. Mazzucco (eds). 248 × 175 mm. Pp 166. Illustrated. 1991. Padua: Piccin Nuova Libraria.

There has been an expansion in the use of lung transplantation for respiratory and combined cardiac and respiratory disease in the past few years. This recent expansion is due largely to the clinical experience and laboratory research of the centres represented in this book. The volume is based on a symposium on chronic respiratory insufficiency held at the University of Padua in 1988. It contains an overview of chronic respiratory failure and a brief chapter summarizing recent developments in extracorporeal support for acute respiratory failure. There is an excellent chapter on lung preservation for transplantation, followed by sections on single, double and combined heart–lung transplantation from recognized authorities in the field. Infectious complications following pulmonary transplantation and a chapter on the pathology of pulmonary biopsy complete the work.

This is a field of major interest to cardiothoracic surgeons, respiratory physicians and intensivists. The book attempts to provide a broad overview as well as highlighting certain areas of topical interest. As a multiauthor collection based on a symposium, the editors have done well to combine each section into a readable and well balanced work. The illustrations are relevant and the bibliography up to date. Recent developments, such as the use of internal mammary-to-bronchial-artery anastomoses for revascularization of left single-lung and double-lung transplants, and the use of unprotected bronchial anastomoses, are not covered, but otherwise it is remarkably up to date. This is an excellent book that has been well produced and attractively presented. I can recommend it to all concerned with lung and heart–lung transplantation.

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Medical Theory, Surgical Practice – Studies in the History of Surgery

C. Lawrence (ed.). 223 × 145 mm Pp. 331 Not illustrated 1992. London: Routledge. £45.

I enjoyed reading this book. The authors have obviously researched their subjects well and presented them in the context they intended to. Many in the surgical field would empathize with their colleagues in the Victorian era after reading selected chapters. I, in particular, found the chapter on Morgagni and 18th-century physical examination rather amusing. Surgery as a craft and science still survives very much on the observant eye, although technological prowess has overshadowed surgical practice in the present time. This book deserves a place in all respectable medical libraries and is definitely recommended reading. My congratulations to the authors.

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Year Book of Vascular Surgery 1992

J. J. Bergan (ed.). 235 × 155 mm Pp 400 Illustrated 1992. St Louis, Missouri: Mosby–Year Book US $59.95

This is the latest edition of the *Year Book of Vascular Surgery*, originally begun in 1986, initially under the joint editorship of Drs John Bergan and Jimmy Yao. It follows the usual excellent format that will be familiar to those who have used this book in the past. For those for whom it is new, this is one of a number of the *Year Book* series that now tackle 44 different medical disciplines. This particular one draws its material from over 100 US and foreign medical and allied health journals. The editors select from these articles of particular interest. Each is presented as a précis of background, methods, results, discussion etc. and is followed by crisp editorial comment. The chapters are divided into various aspects of vascular surgery such as cerebrovascular, venous etc. and there is a subject and author index. It will be appreciated from the above that this is an invaluable addition to the vascular library, as a reference book, for research and for general reading.

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Emergency Vascular Surgery

R. M. Greenhalgh and L. H. Hollier (eds). 250 × 170 mm. Pp 558 Illustrated 1992. London: Harcourt Brace Jovanovich. £80.

This is an exciting book for any practising vascular surgeon. It is written by recognized experts from the world of vascular surgery and genuinely deals with emergency practice. It contains some exciting insights into the latest techniques of transjugular intrahepatic portosystemic stent shunting, as well as thrombolytic therapy for vascular emergencies. There is a good critical review of carotid artery emergencies and even venous emergencies are covered in some detail. The book is a fund of information and I am sure will be a welcome addition to the bookshelves of all vascular surgical departments.

The only errors I was able to find were that my own name had been omitted from one of the references and the name of one of my colleagues had been misspelt. These are very small criticisms of a book that covers over 500 pages and has contributions from 80 authors. Roger Greenhalgh and Larry Hollier are to be congratulated on this valuable and well balanced contribution to vascular surgical knowledge.

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Surgical Secrets

C M. Abernathy and A. H Harken. 229 × 157 mm. Pp. 331. Illustrated 1991. USA. Harvey and Belfus. £20·50.

This book is not, as the title might suggest, a Pandora's box containing those gems of surgical knowledge and practice that are often so elusive and hard to find. It is a book of short questions and answers to help medical students learn the facts of surgery. The whole of general surgery, including cardiothoracic surgery and orthopaedics, is covered in 92 short chapters of a page or two The book contains a wealth of material, quite a lot of which is not essential knowledge, which all but the distinction candidate would find daunting The question and answer method is certainly useful for revising and testing one's knowledge and many candidates taking the final FRCS examination would find it valuable. It is a pity that a volume designed as a pocket book is slightly too large for most pockets

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Lung Biology in Health and Disease. Vol. 50. Adult Respiratory Distress Syndrome

W M. Zapol and F Lemaire (eds) 230 × 150 mm Illustrated 1992. Pp. 586. USA Marcel Dekker. US $150

'Has the patient got ARDS?' is a question that plagues those doctors who practise in intensive care units. The answer depends on the attitudes, knowledge and bias of both questioner and questioned. First defined in 1967 by Ashbaugh, the search for a perfect set of diagnostic criteria has led to a probable underdiagnosis of mild to moderate forms, and a concentration on severe disease with usually complex and life-threatening concurrent illness.

This volume represents a summary of state-of-the-art knowledge of ARDS – or rather, as is certain for all multiauthor texts, the 'state of the art' as it was when written. Information on support, for example, perhaps underestimates the role of posture and does not mention intravenous oxygen exchange or nitric oxide as potential therapy. The chapters do, inevitably, overlap somewhat, but each can be read as an excellent review of one aspect of ARDS. The chapters are well referenced and clearly written, and of a uniform high standard. I particularly enjoyed those on lung mechanics and cardiorespiratory interactions

The reviewer has had to contend with the book being removed surreptitiously on a number of occasions, followed by a suspicious increase in knowledge of ARDS in the unit. I am sure it is an essential reference for those who have a major interest in intensive care and ARDS. Many chapters can also be recommended as an overview for those with a less compelling interest. I will be sorry to see it leave my bookshelf for the unit library

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Anatomic Exposures in Vascular Surgery

G. G. Wind and R. J Valentine (eds). 280 × 215 mm. Pp 490 Illustrated. 1991. Baltimore Williams and Wilkins.

With the increasing proliferation of textbooks on surgery, and on vascular surgery in particular, there has arisen a need for an 'angle' to differentiate the new volume from its antecedents. In the case of *Anatomic Exposures in Vascular Surgery* the angle is that surgical procedures are not described, only the techniques of exposing the vessels most often operated on. The descriptions are clear, concise and supported by a multiplicity of beautiful line drawings – and here lies the strength of the book – drawings from angles and perspectives that are instantly recognizable by the surgeon. While there is a suspicion that most of this has been described at least adequately before, this hardly detracts from the present work, because of its extreme clarity of exposition. The aim of the book 'to describe and illustrate the anatomic relationship of blood vessels' has most certainly been achieved, and clinical references from the American literature are available at the ends of chapters, although the anatomical exposition of the text leading to references on clinical management seems an unusual juxtaposition.

It would be good to have this book in the vascular unit library for occasional reference and for the benefit of surgeons in training. Whether it will appeal to individual vascular surgeons for personal purchase is another matter: one man's meritorious novel concept is another man's gimmick.

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Notices and announcements

3–6 January 1993
Postgraduate Course in Gastroenterology
Oxford, UK
Information Dr D P. Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

7–8 January 1993
Surgical Research Society Meeting
London, UK
Information Professor J R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

5 February 1993
Transjugular Intrahepatic Portocaval Shunts
Toulouse, France
Information Service d'Hépato-Gastro-Entérologie, CHU Purpan, 31059 Toulouse, France

18–20 February 1993
Colorectal Disease in 1993: an International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Room TT-31, Cleveland, Ohio 44195-5241, USA

21 February 1993
Phlebology Review
Lake Buena Vista, Florida, USA
Information North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, California 92024, USA

22–24 February 1993
Sixth Annual Congress of the North American Society of Phlebology on the Advances in Sclerotherapy and the Advances in Surgical and Medical Treatment of Venous Disease
Lake Buena Vista, Florida, USA
Information North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, CA 92024, USA

5–7 March 1993
Impact of HIV Infection on the Gastrointestinal Tract
Bologna, Italy
Information Noema Congressi, Via Lame 24, 40122 Bologna, Italy

12–15 March 1993
7th Congress of the Western Pacific Association of Critical Care Medicine
Hong Kong
Information Ms E Lindsay, Secretariat, International Conference Consultants Ltd, Suite A/B, 16 F, Casey Building, 38 Lok Ku Road, Sheung Wan, Hong Kong

19–20 March 1993
2nd European Congress on Ambulatory Surgery
Brussels, Belgium
Information Dr Cl. De Lathouwer, Brussels One Day Clinic, Nouvelle Clinique de la Basilique, 37–47 Rue Pangaert, B-1080 Brussels, Belgium

31 March–2 April 1993
UICC Kyoto International Symposium on Recent Advances in Management of Digestive Cancers
Kyoto, Japan
Information Professor T Takahashi, Department of Surgery, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602, Japan

5 April 1993
Injury Research Group 1993 Meeting
Milton Keynes, UK
Information Dr R. N. Barton, North-western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

14–16 April 1993
Association of Surgeons of Great Britain and Ireland Annual Meeting
Birmingham, UK
Information Caroline Ross, Association of Surgeons of Great Britain and Ireland, at The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

19–22 May 1993
Eighty-fourth Annual Meeting of the American Association for Cancer Research
Orlando, Florida, USA
Information AACR Office, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, Pennsylvania, USA

7–8 June 1993
8th International Symposium – Applied Physiology in Clinical Respiratory Care
Rotterdam, The Netherlands
Information Dr O Prakash, Thorax Centre BD 164, Dijkzigt Hospital, Dr Molewaterplein 40, 3015 Rotterdam, The Netherlands

8–11 June 1993
World Association of HPB Surgery 1st European Congress of Surgery
Paris, France
Information EHPBS Congress Secretariat, Congress House, 65 West Drive, Cheam, Surrey SM2 7NB, UK

9–12 June 1993
The Endocrine Society 75th Annual Meeting
Las Vegas, Nevada, USA
Information Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

5–8 July 1993
First International and Eighth European Conference on Clinical Hemorheology
Vienna, Austria
Information· Professor E. Ernst, Department of Physical and Medical Rehabilitation, University of Vienna, AKH Wahringer Gurtel 18–20, 1097 Vienna, Austria

6–17 July 1993
Current Practice in Neonatal and Paediatric Surgery
Manchester, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

8–9 July 1993
Surgical Research Society Meeting
Dundee, UK
Information· Professor J R Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

8–10 July 1993
5th South-east European Symposium of Paediatric Surgery
Graz, Austria
Information Professor M E Hollwarth, Department of Paediatric Surgery, University of Graz, Heinrichstraße 31, A-8010 Graz, Austria

19–24 July 1993
Second United European Gastroenterology Week
Barcelona, Spain
Information. Professor J. R Malagelada, Calle Calvet 55–57, 08021 Barcelona, Spain

11–14 August 1993
27th Malaysia–Singapore Congress of Medicine
Kuala Lumpur, Malaysia
Information Organizing Committee, Level 5, MMA House, 124 Jalan Pahang, 53 000 Kuala Lumpur, Malaysia

22–28 August 1993
35th World Congress of Surgery of the International Society of Surgery
Hong Kong
Information. Scientific Secretariat, c/o ISS/SIC, Hauptstraße 63, PO Box 411, CH-4153, Reinach BL 1, Switzerland

15–18 September 1993
Eurosurgery '93
London, UK
Information· Professor J P. S Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

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Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296** · 401–5 or the *Annals of Internal Medicine* 1988, **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1 00 per copy).

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Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results Authors should avoid discursive speculation

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact. Mr J A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references Submissions may be subjected to external review and assessment by the Editorial Board before acceptance The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication

Short notes

These are original observations presented in brief form They should follow the standard format of introduction, methods, results and discussion, but no summary is required Short notes should not exceed 500 words with a maximum of five references and one table or one figure

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 500 words, with no more than five references and one illustration

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support, and (6) the category in which the manuscript is being submitted (original article, case report etc)

Summary

The second page of the manuscript should carry a summary of not more than 150 words It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions

Tables and illustrations

Three copies of all illustrations and tables should be submitted Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s), the top of the illustration should be indicated Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e g 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000 SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg) Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points

References

References should be typed with double spacing and cited in the Vancouver style (see above. Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable Personal communications should be cited in the text, in parentheses The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$ References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s), title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66** 184–6 The sequence for the chapters of a book should be: author(s), chapter title, editors; book title; place of publication, publisher; year of publication; page numbers. For example. Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications* New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78** · 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the *P* value. For example, '$t = 1{\cdot}34$, 16 d.f, $P = 0{\cdot}20$' might be reported. Actual *P* values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Statistical significance should not be confused with clinical significance In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

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Calcium alginate

ACTIVE HAEMOSTATIC SURGICAL ABSORBENT

ALGISTAT Active Haemostatic Surgical Absorbent. **Presentation** Soft white sterile patterned absorbent felt of calcium alginate fibre, incorporating an X-ray detectable strip. **Uses** As an adjuvant in the control of haemorrhage during surgery and to absorb fluids from intra-operative bleeding. ALGISTAT must be removed before the incision is closed at the end of surgery. **Dosage and Administration** There is no difference in the treatment of adults, children or the elderly. ALGISTAT is applied to areas of capillary oozing and venous bleeding. **Contraindications, warnings, etc** Remove ALGISTAT when bleeding has stopped, or when maximum absorbency has been reached. ALGISTAT must be removed at the end of surgery. before skin closure. Animal studies have shown that if calcium alginate is left in-situ on wound closure, a local intense inflammatory response is observed and adhesions will be produced. Although rare, hypersensitivity reactions to the product may occur. ALGISTAT is not intended to replace normal surgical practices for controlling bleeding. The physical characteristics of ALGISTAT differ from that of conventional cotton gauze swabs. It is unsuitable for applications where the latter are employed for their physical characteristics. These include the application of fluids to surfaces, as temporary covers, e.g. over the ends of resected bowel, for the application of traction to tissues, or in "blunt" dissection. **Use in pregnancy** The effect of alginates during pregnancy and lactation has not been studied, but no hazard in their use is anticipated. **Pharmaceutical precautions** Store in a cool, dry place. Not to be resterilised. **Legal Category** ☐P **Package Quantities** 10cm x 10cm. sachet containing 3 absorbents, carton of 10 sachets £75. 10cm x 20cm, sachet containing 2 absorbents, carton of 10 sachets £90. Product Licence No: PL 6079/0009

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LABORATORIES LIMITED

Subsidiary of MERCK & Co., Inc., Rahway, NJ, USA

Marketed in the UK by **BritCair**, a division of C V Laboratories Limited

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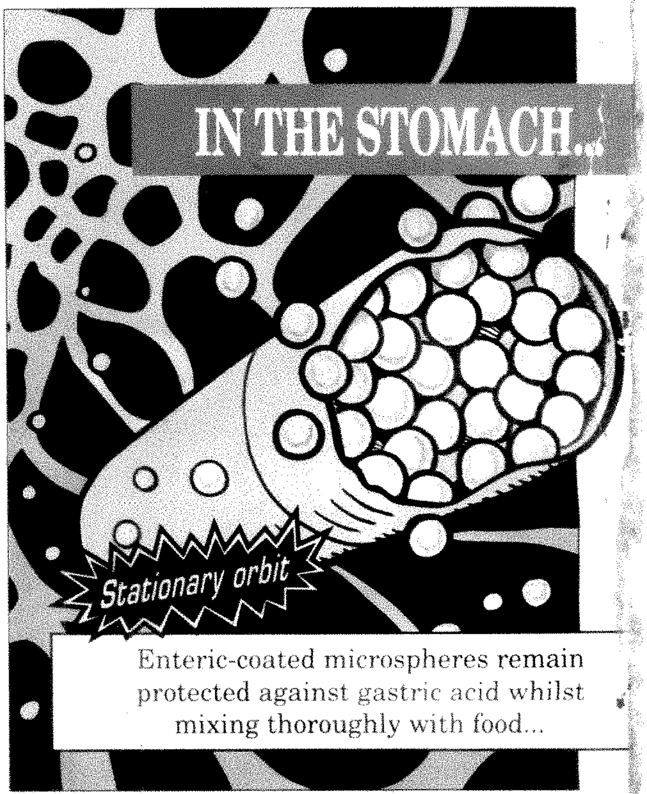
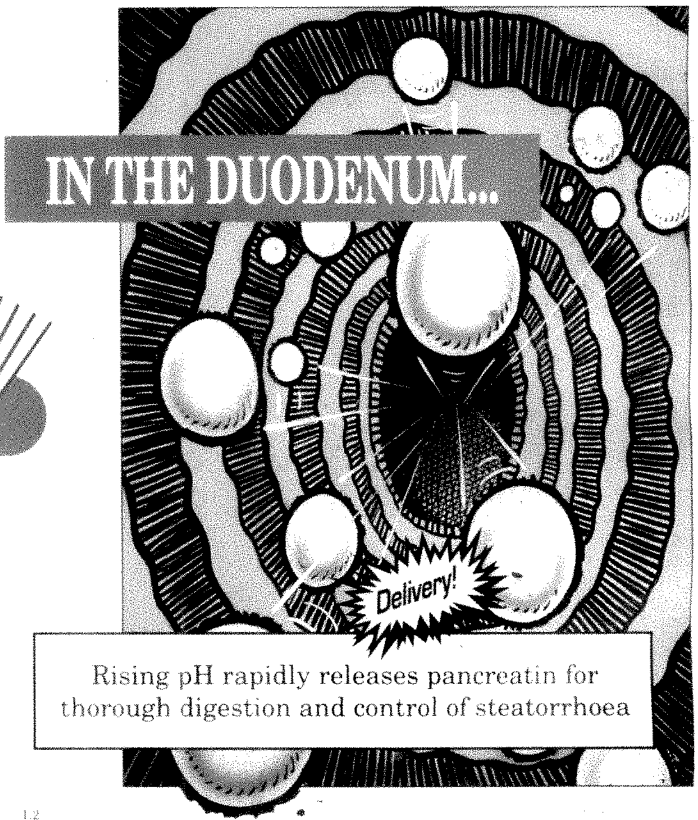
R141/6.92

A NEW
FORCE IN
PANCREATIC
EXOCRINE
INSUFFICIENCY



Enteric-coated microspheres remain protected against gastric acid whilst mixing thoroughly with food...


IN THE DUODENUM...
Delivery!

Rising pH rapidly releases pancreatin for thorough digestion and control of steatorrhoea

New creon® pancreatin 25000

Superior control of steatorrhoea†

† Compared with standard enteric-coated tablets in pancreatic insufficiency[1,2]

Prescribing Information
Presentation: Opaque orange-yellow hard gelatin capsules containing brownish coloured enteric coated pellets of pancreatin, equivalent to:
25,000 BP units of lipase
18,000 BP units of amylase
467 BP units of protease
Available in packs of 50. Basic NHS price £19.50
Indication: Pancreatic exocrine insufficiency.
Dosage and Administration: Adults (including elderly) and children: Initially one capsule with meals, then adjust according to response.
The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with fluid or soft food, but without chewing. If the granules are mixed with food it is important that they are taken immediately, otherwise dissolution of the enteric coating may result.
Contra-indications, Warnings, etc. Contra-indications: Substitution with pancreatic enzymes is contra-indicated in the early stages of acute pancreatitis. Warnings: Use in pregnancy. There is inadequate evidence of safety in use during pregnancy. The product is of porcine origin. Rarely cases of hyper-uricosuria and hyper-uricaemia have been reported very high doses of pancreatin.
Overdosage although not experienced until now, could precipitate meconium ileus equ
Perianal irritation, and rarely, inflammation, could occur when large doses are used.
Product Licence Number: 5727/0006
Name and Address of Licence Holder
Kali Chemie Pharma GmbH, Hans-Bockler-Allee 20, 3000,
Hannover 1, Germany.

References
1. Stead R J et al. *Thorax* 1987; **42**, 533-37
2. Beverley D W et al. *Arch Dis Child* 1987; **62**: 564-68

Further information is available from:
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